



# ANNALS OF INTERNAL MEDICINE

MAURICE C. PINCOFFS

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# ANNALS OF INTERNAL MEDICINE

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JULY, 1940

NUMBER 1

## CLINICAL APPLICATION OF THE THIOCHROME REACTION IN THE STUDY OF THIAMIN (VITAMIN B<sub>1</sub>) DEFICIENCY \*

HARRY J. BORSON, M.D., *San Francisco, California*

A CHEMICAL method for the estimation of thiamin (vitamin B<sub>1</sub>), should have the advantages, as compared to biological assay, of speed, accuracy, cheapness, and ease of performance. The great advantage of biological assay is definite specificity. However, under well controlled conditions the uncertainties of chemical assay may become negligible.

Of the several methods proposed for the chemical estimation of thiamin, the thiochrome method of Jansen<sup>1</sup> has received the most attention. Recently, the method of Prebluda and McCollum<sup>2</sup> as modified by Melnick and Field<sup>3</sup> has been shown to possess a high degree of specificity and accuracy, but the technic as described seems too complex for ordinary clinical purposes. Schultz et al.<sup>4</sup> have developed a fermentation test for vitamin B<sub>1</sub> which apparently is rapid and sufficiently specific for most purposes.

The phycomyces growth method of Schopfer,<sup>5</sup> applied to various materials by Meiklejohn,<sup>6</sup> Bonner,<sup>7</sup> and Rowlands,<sup>8</sup> may prove to be of considerable value as a comparatively simple method of biological assay suitable for clinical investigation.

The purpose of this paper is to relate experiences with the thiochrome method as applied to urine in study of the metabolism of thiamin in normal and thiamin deficient subjects, with special attention to the possibility of diagnosis of thiamin deficiency states.

Using the bradycardia method of bioassay, Harris and his associates<sup>9</sup> showed that the urinary excretion of thiamin depends upon the amount ingested; that subjects on adequate diets excrete in the urine more thiamin than patients with varying degrees of deficiency. In 24 hours normal sub-

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The synthetic thiamin chloride used in this study was furnished by E. R. Squibb and Sons.

jects excreted from 12 to 23 International Units of thiamin on a "normal" diet, and from 36 to 76 International Units after oral administration of a vitamin B concentrate containing 340 I.U. (i.e., about 10 to 20 per cent of the test dose). Patients on inadequate diets, with and without definite deficiency disease, excreted much less; those with frank beri-beri, the least. Using a modification<sup>10</sup> of the original thiochrome method, Westenbrink and Goudsmit studied the urinary excretion of thiamin in normal subjects, in pregnant women with and without manifestations of thiamin deficiency, and in patients with arrested tuberculosis.<sup>11</sup> They demonstrated that the substance (presumably thiamin) estimated by the thiochrome method did fluctuate in amount in the urine just as thiamin would be expected to fluctuate under the various experimental conditions, thus demonstrating a degree of specificity in this method sufficient for clinical purposes at least. The urinary excretion of thiamin was found to be dependent on the amount ingested, and decreased rapidly to a low level in three days with the subjects on deficient diets. An estimate of the degree of depletion could be made by finding the number of oral test doses required for the 24-hour excretion to become normal. Normal subjects usually excreted more than 100 gamma (80 to 300) in 24 hours. Oral administration of pure thiamin in moderate doses (3 to 5 mg.) resulted in increased excretion beginning in the first hour, reaching a peak in the second or third hour, and complete in about five hours. Larger doses often resulted in increases of excretion extending into the second 24-hour period. The per cent excreted in 24 hours varied considerably with the size of the dose and the frequency of administration. About 15 per cent was excreted after a single 3 mg. dose, 8 to 10 per cent after a single 5 mg. dose, 5 per cent after a single 20 mg. dose, and 10 per cent after administration of 20 mg. in divided doses (i.e., the percentage excreted depended upon the size of the individual dose rather than upon the total dose given during the day).

Intramuscular injection gave a maximum excretion in the first hour, with the subsequent excretion about the same as after oral administration when doses of moderate size were used. The larger the amount injected, the greater was the per cent excreted (5 per cent of 1 mg., 10 per cent of 3 mg., 20 per cent of 10 mg.). By the use of parenteral test doses no significant differential in excretion was found between normal and thiamin deficient subjects, so that the parenteral method was considered of no value for diagnosis of deficiency.

Pregnancy was found to exert a marked influence on thiamin excretion, as pregnant women excreted considerably less thiamin than non-pregnant women presumably on similar diets. A group of pregnant women without symptoms referable to thiamin deficiency excreted significant, although sub-normal amounts, both before and after the administration of test doses, while another group with symptoms, of the same economic class, excreted very much less, and often required several test doses before any thiamin was detected in the urine.

Karrer and Kubli,<sup>12</sup> using their modification of this method, found the excretions to be of about the same magnitude as those found by other investigators, the results with the thiochrome method varying by about 20 per cent from the results of assay with the bradycardia method. However, the latter method is hardly sufficiently constant and accurate to serve as the basis for estimating the error of the thiochrome method.

Pyke,<sup>13</sup> using crystalline thiamin and acid-clay adsorbates, found a high degree of correlation between the thiochrome method and bioassay. Ritsert<sup>14</sup> applied the thiochrome method to feces as well as urine, and found 100 to 400 micrograms of thiamin in the feces of normal men in 24 hours. Of a single 10 mg. dose 4 to 6.5 per cent was found in the urine, and 20 to 25 per cent in the feces. The high fecal excretion points to incomplete absorption of large doses.

### METHOD

The method to be described depends upon the following reaction: Thiamin oxidized by the appropriate amount of ferricyanide in strongly alkaline solution is converted quantitatively (Jansen) into thiochrome, which fluoresces intensely blue in ultra-violet light. The intensity of the fluorescence varies with the amount of thiochrome present, and may be measured either with a photo-electric cell<sup>1, 10, 13, 18</sup> or by visual comparison with standards.<sup>12, 14, 15</sup>

Our present technic is as follows: The urine (usually a 24-hour specimen) is collected in 10 ml. of glacial acetic acid. A portion (usually 5 ml.) is diluted with 10 volumes of water to inhibit adsorption of interfering substances,<sup>10</sup> is acidified with glacial acetic acid until acid to congo red, and is then shaken for 10 to 15 minutes with 300 mg. of Lloyd's reagent.\* After filtration by suction, the adsorbate is washed with water acid to congo red, and dried with 95 per cent alcohol followed by ether. Two 100 mg. portions are weighed into glass-stoppered flasks (cork and rubber stoppers would contribute fluorescent substances) and to one portion are added successively 2 ml. methanol, 1 ml. water, and 0.6 ml. 1 per cent potassium ferricyanide. After mixing thoroughly, 1 ml. of 30 per cent sodium hydroxide is added, and the mixture shaken gently for about a minute. The thiochrome formed is extracted by shaking vigorously for a minute with 10 ml. isobutanol (previously saturated with water to avoid variable changes in volume). On standing or centrifuging, the mixture separates into two layers, with the alcohol layer (10 ml.) on top. This may be clarified by filtration (the use of filter papers which furnish fluorescent substances should be avoided) or by drying with anhydrous sodium sulfate, although visual comparison is facilitated by the more even illumination found in the turbid solutions. The suspended water does not interfere with the estimation.

\* Some adsorbent earths lose considerable weight in this procedure, and must be weighed after the adsorption and drying. Our Lloyd's reagent loses no weight.

The second portion of adsorbate is treated in exactly the same way, except that the ferricyanide is omitted. This "blank" contains the non-specific fluorescent substances carried over from the urine, but no thiochrome.

A standard solution of thiochrome is prepared by oxidation of 20 gamma of thiamin chloride without preliminary adsorption, using exactly the same amounts of reagents and the same aqueous volume. Since the aqueous volume is the same in the standard and the unknowns there is automatic compensation for the loss of thiochrome remaining in aqueous solution which is not the case when the standard is prepared with a very small aqueous volume, as in the procedures described by some other authors.\* The standard may now be considered to have the equivalent of 2 gamma of thiamin per milliliter.

A 5 ml. portion of the "test" solution is placed beside a similar portion of the "blank" solution in a simple comparator in which ultra-violet light from a small mercury arc † falls upon the tubes perpendicular to their long axes. Optically matched tubes are used for the two portions. The fluorescence is viewed from above. This procedure has seemed somewhat easier than comparison of the intensities by viewing from the sides or at an angle since the fluorescence appears to be concentrated in a small area. Confusing reflection is therefore avoided. Visible light from the arc is screened out by a filter (Corning No. 586). The reading is made in a darkened room.

If the specimen contains a significant amount of thiamin the "test" solution will have a blue fluorescence as well as the variable amounts of green from normal constituents of the urine, while the "blank" will exhibit only the "non-specific" green. Enough of the standard thiochrome solution (diluted 1:5 with isobutanol for most specimens) is added from a burette to the blank to make the intensities match. Volume changes are compensated for by addition of isobutanol to the "test." The amount of thiamin may then be calculated readily. Duplicate readings within 5 per cent are made easily in assaying pure thiamin, in amounts varying from 0.05 to 3.0 gamma in the 5 ml. isobutanol solution. It is less easy to compare solutions prepared from urine, because of the polychromatic fluorescence (blue through green). This difficulty is eliminated by viewing the fluorescence through a blue color filter.‡

#### USE OF METHANOL

As the work of Jansen and Westenbrink<sup>1,10</sup> has shown, methanol in some manner protects the reaction against excessive concentrations of ferricyanide. If methanol is used as described, 0.6 ml. of 1 per cent ferri-

\* With this procedure the ratio of the concentration of thiochrome in aqueous layer to that in alcohol layer is about 1:2.4.

† The inexpensive "H<sub>4</sub> lamp" manufactured by General Electric and Westinghouse gives very satisfactory results without excessive heat production.

‡ Wratten gelatin filter No. 47 (Eastman) has transmission characteristics suitable for this purpose.

cyanide solution will serve for quantities of pure thiamin varying from 1.0 to 20 gamma (the range tested), with variations of about 10 per cent, which is little more than the error of the actual comparison. When methanol is not used, the amounts recovered are much more variable whether or not preliminary adsorption has been carried out. In preparation of the standards, if methanol is used, the quantities of thiochrome obtained with amounts of ferricyanide ranging from 0.02 to 1.0 ml. of the 1 per cent solution vary not more than 10 per cent. Table 1 shows results in the assay of urine.

TABLE I  
Urine Specimen (Micrograms per 24 Hours)

	1	2	3	4	5	6
With Methanol	365	345	800	500	180	25
Without Methanol	65	170	630	270	95	15

#### ADSORPTION

In an attempt to simplify the procedure, urine was treated without preliminary adsorption (1-5 ml.). Usually the results were a little higher (table 2), indicating minor losses in the adsorption.

TABLE II  
Urine Specimen (Micrograms per 24 Hours)

	1	2	3	4	5	6	7	8	9	10
Adsorbate	210	195	110	102	115	75	30	245	245	85
Urine	250	220	160	92	130	80	30	290	255	95

Under certain conditions readings were inaccurate or impossible unless the adsorption technic was used. The urines of patients taking aspirin, codeine, or quinine, when treated directly produced "blanks" with intense blue fluorescence, often much stronger than that of the oxidized portion. A similar result was obtained in testing urines of a patient with severe pernicious anemia who had not been taking any drugs, and had had no liver extract. This is reminiscent of the difficulties encountered in applying the thiochrome method to assay of liver.<sup>16</sup> That this was not caused by oxidation of thiamin to thiochrome in the blank is indicated by: (1) the intensity of the "blank" fluorescence which may be many times the possible maximum due to thiamin; (2) its independence of the intake of extra thiamin; and (3) its dependence on the intake of the drugs noted, except in the last case in which it may be related to abnormal pigments.

Because of the possible errors in oxidizing specimens without preliminary adsorption, the adsorption technic was adopted as the routine procedure.



## INTERFERING SUBSTANCES

The drugs mentioned above interfere only if the adsorption technic is not used. Red pigments have been found in the urines of pellagrins, often in association with substances, presumably coproporphyrins, which are fluorescent in ultra-violet light and soluble in acid-ether. This pigment, which Watson<sup>17</sup> suggested might be indirubin, is adsorbed by the Lloyd's reagent, which it colors red, and interferes with the reading chiefly by imparting to the "blank" the property of inhibiting the fluorescence of added thiochrome. It apparently is changed in the oxidized portion to a substance which does not inhibit the thiochrome fluorescence.

Bile interferes with the estimation, apparently more by inhibition of the fluorescence of thiochrome than by inhibition of the formation of thiochrome. If the highly colored "blanks" are used in the usual fashion, a large quantity of thiochrome may be added without imparting to the "blank" the characteristic blue fluorescence. If, however, pure isobutanol is used in place of the "blank" solution a comparison may be made, although the results are less accurate. By this procedure thiamin added to urine containing bile is recovered to the extent of about 80 per cent.

These interfering pigments may be removed fairly effectively by preliminary extraction of the urine with an equal volume of isobutanol. About 5 per cent of the thiamin is lost by this procedure. The green-fluorescent substances present in normal urine are not removed by isobutanol or by ether well enough to make extraction worth while, despite the advocacy of the former by other workers.<sup>14, 31 \*</sup>

## RECOVERY OF THIAMIN ADDED TO URINE

Table 3 indicates not only that added thiamin may be recovered adequately, but also that the same quantity of reagents may be used for widely differing amounts of thiamin in urine.

## NORMAL EXCRETION

Table 4 summarizes data obtained by testing a group of interns and laboratory workers whose diets were known to be rich in thiamin. Test doses of 0.1 mg. of thiamin per kg. of body weight were given. This amount was adopted somewhat arbitrarily, but it has given good results in distinguishing various degrees of deficiency. In all subsequent tables the

\* Recently we have used synthetic zeolite (Decalso) as the adsorbent, as suggested by Hennessy and Cerecedo.<sup>18</sup> This has the great advantage of adsorbing practically none of the non-specific fluorescent substances present in normal urine, so that the reading is made much more easily; 500 mg. of finely ground acid-washed (Decalso) are shaken with the urine (diluted 1:40 with water) and treated just as described for the Lloyd's reagent. Recoveries of thiamin added to urine range from 90 to 95 per cent. The red pigment to which reference has been made in the urines of pellagrins is very little adsorbed. The amount of ferricyanide required for the oxidation is much less, but recoveries are practically the same (variation 5 to 10 per cent) over a range of 0.1 to 0.6 ml. 1 per cent ferricyanide. Interference from bile pigments is practically eliminated.

size of the test dose recorded was determined on the same basis unless otherwise stated. The doses were given before breakfast.

In table 4 and all subsequent tables the excretion is expressed as a per-

TABLE III  
Recovery of Thiamin Added to Urine

Subject	Gamma Present	Gamma Added	Gamma Found	Per cent Recovered
D. H.	0.58/15 ml.	1.0	1.51	93
	0.58/15	2.0	2.49	95
H. B.	0.13/7.5	1.0	0.94	81
	0.13/7.5	2.0	1.69	84
	0.13/7.5	3.0	2.46	82
	0.20/10	2.5	2.20	80
	0.20/10	5.0	5.00	96
	0.20/10	7.5	7.20	96
M. C.	1.3/10	1.0	2.2	90
	1.3/10	2.0	3.0	85
	1.3/10	3.0	4.0	89
	1.3/10	4.0	5.0	90
M. S.	0.74/10	5.0	5.4	94
	0.74/10	10.0	10.6	98
	0.74/10	15.0	15.3	97
	1.33/5	2.0	3.24	95
	8.2/10	2.0	10.2	100

TABLE IV  
Normal Subjects

Subject	Gamma 24 Hours Resting	Test Dose mg.	Per cent Excreted 24 Hours	Gamma/100 ml. Urine	Comment
S. A.	200; 290	7	18.1	50	Diet unusually rich in B <sub>1</sub>
E. B.	—	7	15.5	91	
C. F.	—	6.6	8.6-11.6	54-71	
M. F.	110	7	11.1	78	Serial estimations, daily for 2 weeks
D. H.	75; 90	5	11.0	55	
M. B.	—	7	10.4	94	
E. P.	95	5	10.0	21	12 hour excretion; developed catarrhal jaundice shortly afterward
H. F.	—	8	9.8	43	
A. G.	230	6	9.6	45	
J. C.	—	8	9.4	42	
M. B.	—	5	9.3	37	
D. T.	—	6	8.2	61	
F. C.	250	6	7.8; 9.5	28; 52	
P. C.	—	6	8.8	33	
H. B.	110; 220	7.5	6.7	42	
L. G.	155	8	6.0	60	
J. T.	—	6	6.9; 6.1	41	
R. W.	—	7	3.9; 3.5	50	
					5 hour excretion (diet poor past week)

centage of the dose. The intake of thiamin in food is disregarded, since it cannot be estimated accurately, and since the test dose is large in comparison with the dietary thiamin.

Estimations of the excretions after doses of varying amounts have given results substantially in agreement with those found by other investigators; that is, the larger the dose administered orally, the smaller the per cent excreted. Westenbrink<sup>10</sup> thought this to be the result of increased destruction of thiamin in the tissues. Borsook,<sup>19</sup> using thiamin containing radioactive sulfur, showed that a large amount of the thiamin administered is destroyed in the tissues, the sulfur being excreted as ethereal sulfate. The work of Ritsert<sup>14</sup> showed that the feces contain as much as 25 per cent of a 10 mg. dose. Schultz et al.<sup>4</sup> showed that in animals fecal vitamin B<sub>1</sub> was considerably increased by moderate doses of thiamin by mouth. It appears, therefore, not only that a large dose is incompletely absorbed, but also that an excess is rapidly destroyed.

On the other hand, the percentage excreted after intravenous administration increases with increasing doses: about 15 per cent after 3 mg., 20 to 30 per cent after 7 to 10 mg., 50 per cent after 30 mg., and 80 per cent after 50 mg. By far the largest part of the excreted thiamin is found within the first hour.

It is apparent that thiamin is utilized more efficiently in small doses given frequently, either orally or parenterally, than in large single doses.

The data in table 5 are typical of 24-hour excretions after a long period of dosage with crystalline thiamin or crude concentrates given in divided doses.

TABLE V  
Excretions after Long Continued Administration of Vitamin B<sub>1</sub>

Patient	Dosage and Duration	Excretion Gamma per 24 Hours	Per cent of dose
L. B.	200 I.U.* twice daily 10 days	400	39
C. S.	200 I.U. twice daily 3 weeks	400	39
L. B.	200 I.U. thrice daily 2 weeks	500	25
E. R.	200 I.U. thrice daily 10 weeks	605-760	30-38
F. T.	200 I.U. thrice daily 5 weeks	690	35
L. G.	200 I.U. thrice daily 3 weeks	515-680	26-34
E. L.	200 I.U. thrice daily 4 weeks	550	28
E. S.	3 mg.† thrice daily 3 weeks	1300-1680	14-19
F. B.	3 mg. thrice daily 3 weeks	2100	23
A. H.	3 mg. thrice daily 2 weeks	1130	12
E. E.	1 mg. thrice daily 4 weeks	760	25

\* B Complex.

† Synthetic thiamin chloride.

It has been shown<sup>10</sup> that in normal subjects on a thiamin-poor diet for two or three days the 24-hour excretion was reduced to 40 micrograms. It appeared, therefore, that estimation of the excretion without administration of a test dose would in many instances indicate only the adequacy of the diet

during the past few days. Therefore, as a routine procedure in the out-patient department where collection of more than one 24-hour specimen would be difficult, usually only the excretion after administration of the test dose was estimated. Tables 5 to 16 summarize data obtained on several groups of patients. In most cases a detailed dietary history was obtained, but the well known inaccuracy and variability of data on the thiamin content of foods make it presumptuous to assign figures to the probable thiamin content of the diets. The term "good" indicates a diet obviously good, in which no important source of calories is thiamin-poor; "poor" indicates a diet so low in thiamin that one might reasonably expect to find more or less obvious manifestations of thiamin lack; and "fair" indicates the broad range between these extremes.

### THYROTOXICOSIS

Tests were carried out on thyrotoxic patients who had been in the hospital for about a week, on very good diets (see table 6). In the study of

TABLE VI  
Patients with Thyrotoxicosis Tested During the Period of Pre-operative Care

Patient	Diet	Resting 24 hrs.	BMR	Dose mg.	Per cent Ex- creted	Gamma/ 100 ml. Urine	Comment
M. W.	Poor	—	—	5	2.1	16	Auricular fibrillation; congestive failure; pneumonia
P. J.	Fair	13	44%+	6	3.0	13	Apathetic; cardiac damage; post-operative hypothyroidism
V. B.	Fair	—	38%+	5	3.0	15	Auricular fibrillation
L. C.	Fair	—	58%+	5.2	3.6	7	Anorexia; post-operative hypothyroidism
A. B.	Fair	80	45%+	6	4.3	26	Recent improvement in appetite and weight
M. P.	Fair	—	85%+	4	4.7	19	Emaciated; disoriented; mild anemia
H. J.	Good	40	31%+	5	4.8	7	Anorexia; moderate anemia
G. K.	Good	100	42%+	7	4.9	8	Moderate alcoholic; rapid weight loss
M. P.	Fair	150	64%+	4	5.0	9	Emaciated; cardiac damage
C. H.	Fair	30	29%+	6	5.2	13	Marked asthenia; cardiac damage
H. C.	Good	120	46%+	7	6.3	37	Cardiac damage
T. C.	Good	—	66%+	6	6.5	13	Excellent appetite; marked weight loss
L. W.	Fair	8	47%+	—	—	—	Well controlled diabetes; asthenia; anorexia

these patients several factors of importance were noted. Most of them excreted very large quantities of urine, up to four and five liters daily. Many had been satisfying their increased appetites by increasing considerably their intakes of carbohydrate food, often in the form of vitamin-poor candy and

pastry. It is thought that the requirement for thiamin depends either upon the total caloric intake<sup>20</sup> or upon the intake of carbohydrate,<sup>21</sup> so that, despite a fairly good intake of protective foods, the production of mild deficiency in these patients was believed to be related in part to an uncompensated excess of carbohydrate. A comparison of this group with the normals reveals a moderate decrease in the percentage of thiamin excreted by the thyrotoxic group. That this is not a complete picture of the degree of deficiency is suggested by the differences between the groups noted in the columns "gamma/100 ml. urine." Cowgill et al.<sup>22</sup> showed that dogs subjected to diuresis developed signs of B<sub>1</sub> deficiency earlier than dogs on the same diet without diuresis. It might be reasonable, then, to suppose that the percentage of the standard test dose excreted by normally saturated persons excreting large volumes of urine would be somewhat higher than that of normals excreting normal amounts of urine; and that, in estimating the degree of thiamin saturation, the urinary volume as well as the per cent excreted must be taken into account.

Support for this hypothesis was provided by serial estimations carried out on some of the subjects. Two normal subjects excreting 1000 to 1500 ml. of urine daily took the standard test dose daily for a week. In both cases the excretion remained about the same from day to day, i.e., 8 to 11 per cent. The excretion of the thyrotoxic patient, T. C., whose urinary volume was consistently from 3000 to 5000 ml. did not "level off" until an excretion of 17 to 22 per cent was reached. Shortly before operation he voluntarily reduced his fluid intake to from 1500 to 2000 ml. and the excretion dropped to from 10 to 10.9 per cent. Similar results were noted in several other patients. An alternative explanation, not as yet supported by experiment, might be impairment of the liver function in thyrotoxicosis resulting in decrease in the phosphorylation of thiamin with consequent elimination in the urine. On the other hand, in patient A. B. whose urinary volume ranged about 1000 ml. the excretion "leveled off" at 12 per cent.

Within the normal range of urine volume (750 to 2000 ml.) little differences in excretion are noted.

#### TYPICAL THIAMIN DEFICIENCY NEURITIS (Table 7)

In three patients, hospitalized for treatment for severe alcoholic neuritis, in whom it was possible to make daily estimations, it was found that excretions approaching the normal occurred after 60 to 100 mg. of thiamin had been given in doses of 3.3 mg. two or three times a day together with a high vitamin diet. In from 17 to 25 days the excretions "leveled off" at from 17 to 26 per cent of the dose. (These high percentages, it must be remembered, are of small doses given frequently, and are not comparable to the lower percentages found with the standard test doses.) The total doses given before the "leveling off" occurred amounted to from 100 to 125 mg. One may not conclude that these figures represent the total deficit, since it

may be that in chronic alcoholism with possible liver damage there is a decrease in the ability to convert thiamin into cocarboxylase for storage and utilization. The hypothesis that liver damage increases the excretion of thiamin is supported by serial studies in three patients with hepatic cirrhosis in whom the excretions "leveled off" at from 17 to 26 per cent of the standard single test dose given daily. In none of these patients did the urine output ever exceed 1000 ml., so that diuresis played no part in these high excretions. Ochoa and Peters<sup>29</sup> and Westenbrink and Goudsmit<sup>16</sup> have shown that after parenteral administration conversion of thiamin into cocarboxylase takes place largely in the liver and kidneys.

TABLE VII  
Patients With Frank Neuritis Caused by Nutritional Deficiency

Patient	Resting Gamma/24 hrs.	Test dose mg.	Per cent Ex- creted 24 hours	Gamma/100 ml. urine	Comment
N. J.	0	10	0.2	5	Alcoholic; pellagra Alcoholic; "wet beri-beri"; had had 33 mg. thiamin orally prior to first test.
R. H.	—	3.3 Twice daily (under treatment)	0.3	2	
L. D.	—	6	0.3	1.4	Alcoholic; psychosis
D. D.	0	—	—	—	Alcoholic
C. A.	0	5	0.9	7	Alcoholic; anemia; osteoporosis with pathological fracture
T. V.	—	6	1.0	15	Chronic neuritis; moderate alcohol; high vitamin diet two weeks
F. D.	25	11	1.5	7	Mild "post-influenzal neuritis" 4 weeks; well in 48 hours with thiamin orally
K. H.	25	6.7	3.6	26	Mild long-standing "alcoholic neu- ritis" slowly improving with high vitamin diet
H. M.	—	6	2.7	13	Alcoholic neuritis 2 years; no alcohol, fair diet past year, with slow im- provement

#### PERIPHERAL NEUROPATHY OF UNCERTAIN NATURE OR CAUSE

The group in table 8 requires special comment because of the frequent use of the term "neuritis" to describe almost any type of pain or nervous system symptoms. These patients were all carefully examined by the regular staff of either the Neurology or the Neuro-Surgery Departments of the University of California Clinic, and were all considered to have definite disease of the peripheral nervous system without disease of the central nervous system. No patients with tic douloureux were included in this group.

Eight of the 25 patients excreted 4 per cent or less of the test dose, and of these, four experienced definite relief after thiamin feeding. Patient S. F. is particularly interesting. A middle-aged well controlled diabetic, she had been for several years on a well balanced diet and regular insulin. Eighteen months prior to the first test she had developed the habit of drinking large amounts of fluids (no alcohol), and habitually had excreted 4 to 6 liters of urine daily. Nine months later, three months after changing to crystalline insulin, progressively severe paresthesias of the hands began to interfere with her work of packing cookies. Various medications used were

TABLE VIII  
Patient With Peripheral Neuritis of Uncertain Nature or Cause

Patient	Diet	Area Involved	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Comment
T. E.	Poor	Neck; arms; pain, hypesthesia	4	0	0	"Scalenus anticus syndrome" unrelieved by operation; general health, but not pain, improved by thiamin orally
A. H.	Poor	Arms, hands; pain, paresthesias	5.0	1.2	7	Pain, paresthesia, anorexia, strength imp. on thiamin
J. S.	?	Sciatic pain	7	1.1	15	Psychosis; no thiamin given
C. B.	Fair	Pain arms and legs	8	1.5	8	Controlled diabetes; pains cured by thiamin 2 mg. thrice daily for 2 weeks
L. O.	Fair	Multiple; pain, anesthesia, contractures	12	2.2	43	Followed extraction infected teeth and tonsillitis; not improved by thiamin orally and parenterally
F. E.	Poor last 2 wks. only	Brachial plexus;	8	2.6	14	Recent alcoholic excess to relieve pain; not improved by thiamin
L. R.	Poor	Right arm and leg pain and paresthesias	5	3.6	10	Marked relief pain and general health with thiamin 3 mg. daily orally for 3 weeks
D. B.	Good	Pain arm; tremor	5	3.8	14	Pain and tremor markedly improved on thiamin 3 mg. thrice daily
S. F.	Good	Hands. Marked paresthesias hyp- peresthesia	5	4.2	4	See below
G. M.	Fair	Arms, back	11	4.6	41	Probable osteo-arthritis. No improvement on thiamin 3 mg. thrice daily
C. L.	Poor	Sciatic pain	5	5.2	14	Multiple neurofibromatosis; general osteo-porosis; no thiamin given
F. P.	Good	Arms, hands; paresthesias; hyp- esthesia	7	6.1	40	Marked cervical lordosis; no thiamin given
C. A.	Good	Sciatic pain	6	6.4	29	Well controlled diabetes; equivocal relief from thiamin
N. A.	Good	Sciatic pain	9	6.8	29	Mild diabetes; no thiamin given
R. S.	Good	Hands, feet; paresthesias	5	7	32	No relief from oral and parenteral thiamin, B complex, liver, in large doses for one year
J. T.	Fair	Arms; pain, hypesthesia	9	7.1	18	Possibly traumatic; works as lather; no thiamin given
R. B.	Good	Neck, ulnar arm pain, hypes- thesia	7	7.2	14	Cervical osteo-arthritis unrelieved by thiamin 3 mg. daily for one month
A. D.	Good	Peroneal, anesthesia	7	7.8	23	Probably traumatic; no thiamin given
B. H.	Good	Supra- and infra-orbital pain	9	7.8	35	Probably caused by sinusitis
B. G.	Fair	Arm pain, hypesthesia	5	8.4	36	"Scalenus anticus syndrome"
L. H.	Good	Facial pain	5	9.2	25	Severe facial neuralgia with hemihypertrophy
F. B.	Excellent	Arms, legs	6	16.7	71	Probably spinal osteo-arthritis
D. S.	Excellent B sup.	Legs, feet	1	23	79	Treated 1 year with large doses thiamin and B complex orally and I.V. without improvement.
B. M.	Good	Acroparesthesia; 6 mos. pregnant	4 times daily			
E. D.	Good	Pain arm	5 mos. 8 5	9.7 9.7	51 26	No relief from thiamin 3 mg. 4 times daily for three weeks No relief from thiamin 2 mg. thrice daily for 3 weeks

ineffective and for seven months she had never been free of the symptoms. On February 2, 1939 she excreted 4.2 per cent of the standard test dose in 5.1 L. of urine. Two mg. of thiamin given three times a day brought *complete* relief within one week. The dose was then reduced to 1 mg. twice daily. On March 6, on the same dosage, she excreted 600 micrograms of thiamin in 4.5 L. of urine (30 per cent). On March 17, the paresthesias recurred, and on April 10 she excreted 1600 micrograms in 4 L. On increasing the dose to 2 mg. thrice daily she again experienced complete relief in five days, and has since (September 1939) been completely free of symptoms. On April 17, the excretion was 2,650 micrograms in 2.7 L.; on May 1, 1500 micrograms in 2.9 L.; on June 1, 2400 micrograms in 3 L.

The diabetes remained under excellent control throughout the period of observation. It is apparent that her requirement for thiamin is much greater than normal. This may be associated in some manner with unknown metabolic disturbances related to the diabetes; it is probable that the diuresis contributed to the relative deficiency. Reference has been made already to the work of Cowgill on the influence of diuresis on the development of thiamin deficiency. Work is in progress to elucidate a possible relationship between the zinc present in crystalline insulin and the thiamin requirement in man.

Patient B. M. presented the problem of progressively severe acroparesthesias beginning in the third month of pregnancy. Until her high excretion was known, she was considered to have thiamin deficiency disease. No relief, however, was obtained from feeding thiamin in doses of 3 mg. thrice daily for three weeks, thus supporting the conclusion drawn from the excretion studies that thiamin deficiency was not the cause of the symptom.

#### MULTIPLE SCLEROSIS

Most of these 14 patients (table 9) had severe, well-defined multiple sclerosis. Many were mentally so deteriorated as to make adequate nutrition difficult. In only the first patient was an attempt made to give thiamin in large doses parenterally. Although there appeared to be definite improvement following the injections, the follow-up of this patient has been too short for definite opinion as to the result of the treatment. In some of the patients with low excretions, small doses of thiamin or vitamin B complex by mouth led to improvement in appetite, a sense of well-being, and strength—all compatible with our knowledge of the effects of the vitamin in deficiency states, and not necessarily reflecting change in the primary disease.

Of the 14 patients, seven (50 per cent) excreted less than 4 per cent of the test dose, and four (29 per cent) had some symptomatic improvement from the use of thiamin.

#### DORSOLATERAL SCLEROSIS

As indicated in table 10, the few patients with Addisonian anemia and dorsolateral sclerosis had subnormal excretions with the exception of one



TABLE IX  
Patients with Multiple Sclerosis

Patient	Diet	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Comment
F. T.	Poor food faddist	6	0.5	2	Duration 2 years; severe G. I. symptoms; improved appetite, weight, strength, co-ordination after 6 injections of 10 mg. thiamin; 1 mo. later symptoms became worse despite use of B complex orally (approx. 2 mg. daily) lost weight; again improved after further injections.
R. J.	Poor	6	1.5	6	Unsteady gait 8 years; severe paresthesias; appetite and strength improved on thiamin 1 mg. thrice daily
C. S.	Poor	6.6	1.6	6	Improved appetite, coördination on thiamin 1 mg. thrice daily
J. T.	Poor	7	2.1	8	Duration 5 years, not severe; no improvement on thiamin 1 mg. thrice daily
L. O.	?	6	2.3(5 hrs.)		Markedly deteriorated; no improvement on thiamin 2 mg. thrice daily
D. K.	?	5	2.3(5 hrs.)		Markedly deteriorated; results of thiamin therapy unknown
F. B.	?	5	2.7	30	Markedly deteriorated; slight improvement strength on thiamin
P. P.	Fair	7	5	35	Duration 1 year; severe paresthesias; effect of thiamin unknown
J. H.	Fair	5	5.8	23	Duration 5 years; markedly deteriorated
E. W.	Fair	6	5.8	27	Effect of thiamin unknown
G. S.	Good	8	8.3	70	Possible slight improvement prior to testing during a year of therapy with liver and B complex
J. R.	Excellent Recent B supplement	9	8.5	39	No improvement with thiamin 3 mg. thrice daily 4 months
W. S.	Good	6	9.4	39	Progressive deterioration while taking thiamin 1 mg. thrice daily 5 months
S. J.	Good yeast supplement recently	7	11.1	97	Progressive disability despite large doses of yeast 1 year

TABLE X  
Patients With Dorso-Lateral Sclerosis, Achlorhydria, and Addisonian Anemia

Patient	Diet	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Comment
J. L. V.	Fair	5	0.4	4	Severe untreated P.A.; classical C.N.S. manifestations
W. A.	Fair	9	3.6	30	Severe untreated P.A., very mild neurological manifestations
J. A.	Fair	6	3.8	22	Moderate anemia; definite neurological disease of moderate severity
H. Y.	Fair: Recent liver therap.	8	8.2	75	Inadequately treated 3 years; neurological manifestations 1 year

patient who had had crude liver extract parenterally within a few days of testing.

Harris et al.<sup>9</sup> have found subnormal excretions of thiamin in several patients with dorsolateral sclerosis, some with and some without anemia. Van der Scheer and Koek<sup>23</sup> found both clinical and histological evidence of peripheral nerve disease in pernicious anemia. It is possible that part of the neurological picture of Addisonian anemia is caused by thiamin deficiency, with functional change in peripheral nerves. This might contribute to the favorable results reported in treatment of dorsolateral sclerosis with synthetic thiamin.

### CENTRAL NERVOUS SYSTEM SYPHILIS

All patients in this group (table 11) had been receiving the usual treatment for central nervous system syphilis for from six months to five years. In all cases the diagnoses were confirmed by the usual clinical and laboratory tests. Most of the patients were on relief. Allowing for this fact, with its implications of a restricted dietary, there still seemed to be a significant discrepancy between the dietary histories and the states of "saturation" with thiamin as indicated by the excretions. Little is known of the effects of chronic infection on the thiamin requirement, and nothing is known of the effect of heavy metals, which these patients were receiving constantly.

Of the 15 patients, 12 (80 per cent) excreted less than 4 per cent of the test dose. Seven of these had definite improvement in general health, neurological symptoms, or both following oral administration of moderate doses of thiamin. Patients with definite mental deterioration or euphoria were not recorded as "improved," regardless of their statements. There was no obvious relationship between type and duration of antiluetic therapy and improvement on thiamin feeding.

Reese and Hodgson<sup>24</sup> have reported improvement in the neurological status of patients with untreated central nervous system syphilis after administration of vitamin B complex. In many patients of our group, some symptoms that had been attributed simply to the infection were specifically cured by thiamin feeding. This fact and the low excretions found, indicate that thiamin deficiency contributed to the clinical picture.

### TIC DOULOUREUX

Patients with facial neuralgias not typically tic douloureux were excluded from this group (table 12). The excretions in this group indicate moderate to mild degrees of deficiency. It is, of course, impossible to assert that this undersaturation is chronic, but dietary histories have indicated no profound recent changes in the diets. Of the nine patients whose excretions were estimated, four excreted less than 4 per cent, six less than 5 per cent, and seven less than 6 per cent.

TABLE XI  
Patients With Luetic Disease of the Central Nervous System

Patient	Diagnosis	Diet	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Comment
C. B. C. G.	Paresis Tabes, very severe formication and pain, optic atrophy, lassitude	Unknown Fair	6 6.6	0.5 0.7	6 2.5	Rapid deterioration Striking improvement in paresthesias, facial pain, constipation, general health on thiamin 1 mg. thrice daily 5 weeks. No improvement in vision
D. C.	Tabes; typical hyperventilation alkalosis, psychoneurosis	Poor	6	1.1	5	No improvement with thiamin 6 weeks; paresthe- sias typically relieved by ammonium chloride
H. H.	Tabo-paresis	Fair	7	1.3	8	Prog. ataxia and mental deterioration on thiamin 1 mg. thrice daily
A. F.	Unclassified; optic atrophy, facial pain (not "trigger")	Fair	6	1.7	8	Facial pain definitely improved on thiamin 1 mg. thrice daily 1 month
P. C.	Tabes; Charcot knee; pains and paresthesias; constipation; urinary retention; anorexia	Poor	6	2.0	10	On thiamin 1 mg. thrice daily 10 weeks, definitely improved weight, strength, defecation and urination, pain and numbness in legs
G. C.	Tabes; hyperventilation alkalosis	Poor	6	2.1	5	Improvement in paresthesia on thiamin; possible psychologic effect
T. H.	Tabes; lightning pains	Fair	7	2.5	18	Improved after pyrotherapy, no thiamin given
L. M.	Tabes; pains; Charcot knee; optic atrophy	Fair	8	2.5	28	No improvement, thiamin 1 to 2 mg. thrice daily for 10 weeks
G. T.	Tabes; aortitis	Unknown	7	3.3	18	Equivalent imp. pains and paresthesias on thiamin 1 mg. thrice daily
A. C.	Tabo-paresis; sciatic pain	Poor	4	3.4	7	Pain markedly imp. on thiamin 1 mg. thrice daily 4 weeks
C. S.	Unclassified; numbness and dysesthesias leg	Fair	6	3.3	19	Imp. gen. health, but not neurol., on 2 mg. thrice daily 3 months
O. S.	Tabes; Charcot knee, severe pain	Good	7	7.3	26	Prog. worse 6 mos.; no thiamin given
J. W.	Tabes; paresthesias; recurrent malaria (therapeutic)	Good	5	7.8	19	No improvement on thiamin 1 mg. thrice daily for 10 weeks
A. H.	Tabes	Good	7	12.5	35	

Patient	Diet	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Comment
C. G., F. 34. Onset October 1937. No relief after caring for focal infection. Alcohol injection never attempted. No long remissions and no long periods of constant pain	Fair	5.4	2.0	22	Thiamin, 3 mg. thrice daily started September 1938. Improvement began in one month, and pain completely gone in 3 months. Discontinued thiamin December, 1938. Attacks recurred March, 1939, and thiamin was resumed immediately. Pain was slightly improved in 5 weeks, completely gone in 3 months. Now free of pain for 4 months. During first period took ammonium chloride as well as thiamin, but in second period took only thiamin
M. B., F. 42. Classical tic 14 years. Relief for 4 years after alcohol injection, ending in present recurrence of 16 months' duration; with no day free of severe attacks. Slight relief from trethylene during attacks	Good	7	2.9	24	May 1939 started thiamin 2 mg. five times a day. In two weeks noted considerable improvement, stating that she had not felt so well for the past 16 months. Three weeks later attacks still well defined, but very mild. No trethylene used after first week of thiamin therapy. Practically free of pain 8 weeks after starting thiamin. Concomitant relief of "neuralgia" in shoulder. No recurrence of facial or shoulder pain within three months.
V. B., M. 53. Duration 8 years. Remissions infrequent and short past 3 years. Almost constant pain past 5 months	Fair	5	3.0	10	Thiamin 3 mg. thrice daily started October 1939
F. K., F. 37. Duration 13 years, with frequent remissions lasting 2 months to 1 year. Last remission for 6 weeks, until 2 weeks ago. Has extensive infection in teeth and sinuses	Poor	5	3.4	12	Thiamin not given pending results of treatment of dental infection. Four months later stated that extractions of teeth was followed by a remission
C. E., M. 62. Duration 11 years. Relieved for 1 year after alcohol injection. Severe recurrence one month ago in June, 1939	Good	6	4.5	15	On thiamin 3 mg. thrice daily. Noted slight improvement in severity within 4 weeks. No further information available as yet
W. C., F. 70. Duration 15 years. Temporary relief twice after alcohol injection. Last attempt at injection failed. Present attack 15 months' duration with almost constant pain and exacerbation set off by trigger mechanism. Also has some residua of hemiplegia that followed cerebral thrombosis (?) 3 years ago	Fair	5	4.8	16	Thiamin 3 mg. thrice daily, started May 1939. After 7 weeks general health markedly improved. Pain still very severe, but altered in character to a burning sensation. In 10 weeks having occasional days free of pain, and severity of pain definitely lessened. After 4 months was free of pain for about 2 weeks, then relatively mild pain recurred only on chewing, after dose of thiamin was reduced to 5 mg. daily

TABLE XII—Continued

Patient	Diet	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Comment
<i>J. R., M. 44.</i> Duration 8 years. Remissions lasting 2 to 8 weeks about twice a year. Remissions shorter past 2 years. Most severe attacks in August every year. Present attack of 8 months' duration. Unsuccessful attempt at alcohol injection December, 1938	Good	7	5.1	24	Thiamin 3 mg. thrice daily. In 2 weeks pain and "trigger" sensitivity less severe. In one month pressure in "trigger" area caused only mild pain. By July 1939, completely free of all but momentary mild twinges of discomfort, hardly to be called pain. No attacks throughout August or September or to the present (October 1939)
<i>I. C., F. 45.</i> Duration about 12 years. Remissions for 1-4 weeks 3 or 4 times a year. Almost constant pain past six months	Fair	5	5.6	55	Thiamin 3 mg. thrice daily. Started September 1939. No further data yet available
<i>M. P., F. 66.</i> Duration 5 years. Remission for 3 months 4 years ago. No long remissions since. Free of pain for total of only 3-5 weeks in past 2 years. Also, has goiter and auricular fibrillation, with moderate dyspnea and palpitation	Good	6	10.6	32	Thiamin 3 mg. thrice daily. Started July 1939. Pain progressively less severe after 2 weeks, and practically free of pain in 5 weeks. No real attacks for 4 weeks (to September 1939). Also noted increase in strength and lessening of dyspnea and palpitation
<i>F. B., F. 64.</i> Duration 8 years. Temporary relief after 10 alcohol injections, one lasting 3 months 3 years ago. Last remission December 1938 for 6 weeks. Almost constant pain since February 1939	Good	—	—	—	Started thiamin 3 mg. thrice daily. Within a week radiation of pain was less extensive. After 2 weeks attacks were shorter. In one month stated that she was "75 per cent better." Former "trigger" zones now devoid of sensitivity. Concomitant increase in general strength, vitality, ambition
<i>W. R., M. 64.</i> Duration 17 years. Used very large amounts of trethylene, with slight relief, for years. Remissions only partial, lasting 1-12 weeks. Last remission lasted 6 weeks, ending 3 months ago. Previous remission lasted 4 weeks one year ago. Used small amounts of vitamin B complex for 7 months (until 9 months ago) with indefinite improvement in severity of attacks	Fair	—	—	—	September 1939 started thiamin 10 mg. subcutaneously and 3 mg. orally daily. 11 days later had sufficient improvement to allow good sleep. Three weeks after beginning thiamin practically free of pain and twitches, and all trigger zones could be prodded with impunity. Now free of symptoms for one month

Because of the irregular course of the disease, one must be very cautious in interpreting the results of treatment, but at present there seems to be ample reason for regarding the effect of thiamin treatment as encouraging. A later complete report will deal with the results in this group of patients after sufficient time has elapsed for an accounting of the probabilities of remissions, etc., as factors involved in the improvement. Borsook and his associates<sup>25</sup> found remarkable and sustained improvement in a large group of patients with this disease. They gave large doses of thiamin parenterally and vitamin B complex by mouth. Most of about 25 per cent of patients not improved subsequently had significant improvement after the administration of large doses of a concentrated liver extract. We have limited our treatment to synthetic thiamin by mouth, hoping to establish the rôle of this substance. The fact that improvement may not begin for several months cannot be adduced as evidence that thiamin is not the effective agent, since it is well known that the curative effect of thiamin may be slow in neuritis definitely attributable to thiamin deficiency that has lasted for a considerable time. If deficiency disease lasts long enough, structural change is superimposed upon the initial functional (chemical) disorder.

#### MISCELLANEOUS DISEASES OF THE CENTRAL NERVOUS SYSTEM AND MYOPATHIES

This group (table 13) was added simply for comparison. It is of interest that patient J. O. who was considered to have advanced Friedreich's ataxia experienced remarkable improvement in coördination and muscle power after a few months of thiamin feeding, so that he was able to care for himself and even drive a car, formerly beyond his capacity. For a few weeks he also took small amounts of vitamin B complex of unknown nature.

#### RHEUMATOID ARTHRITIS

In general, patients with rheumatoid arthritis (table 14) excreted amounts compatible with their status of "saturation" with thiamin as indicated by dietary history, that is, many of them were undersaturated, as one might expect in any group of the same economic level and food habits. In one patient, M. R., a middle-aged woman with chronic "mucous colitis" who had taken for months a supplement of about 150 I.U. of thiamin daily, the excretion was much lower than might be expected. It is probable that this is related to the diarrhea (see below). No systematic effort was made to study the responses of these patients to thiamin feeding. Of the 24 patients, 11 (46 per cent) had excretions either less than 4 per cent of the test dose or under 50 micrograms without the test dose. Low excretions (under 50 micrograms) were also found in four patients with acute rheumatic fever, not included in the table.

TABLE XIII  
Patients With Miscellaneous Diseases of the Central Nervous System: Myopathies

Patient	Diagnosis	Diet	Resting Gamma/ 24 hr.	Dose mg.	Per cent Ex- creted	Gamma/ 100 ml. Urine	Comment
C. J.	Epilepsy	Fair	—	5	4.8	22	Yeast suppl. until 1 week ago Equivocal imp. with thiamin 1 mg. thrice daily
J. C.	Post-traumatic epilepsy	Good	—	6	8.8	33	
D. H.	Epilepsy	Good	90	5	11	55	
D. R.	Degen. dis. cerebellum with con- vulsions	Fair	—	2	7.2	18	
M. D.	Lateral sclerosis	Good	170	—	—	—	Progressively worse on B complex 6 mos.
R. W.	Amyotrophic lateral sclerosis	Good	—	6	6 (5 hours)	45	
J. O.	Friedreich's ataxia	Poor	20	7	1.6	20	Definite marked imp. on 2 mg. thiamin thrice daily in 6 mos.
I. S.	Progressive spinal atrophy	Fair	—	7	3.7	30	Slightly better in 3 mos. on B complex No improvement. Thiamin 2 months
L. T.	Progressive muscular dystrophy	Fair	65	5	7.3	45	
I. S.	Myotonia dystrophica	Fair	60	6	4.1	13	No improvement, thiamin and B complex 4 mos., progression of nervous manifestations
E. A.	Myasthenia gravis	Fair	15	7	3	20	
M. G.	Acetanilid poisoning; prog. degen. cord and possibly periph. nerves	Fair	30	7	6.3	28	
F. C.	Chorea major	Fair	59	6	3.4	7	

TABLE XIV

Patients With Active Rheumatoid (Atrophic) Arthritis

Patient	Diet	Dose mg.	Per cent Excreted	Gamma/100 ml. Urine	Resting 24 Hours	Comment
M. G.	Poor	—	—	—	40	
E. H.	Poor	—	—	—	32	
O. M.	Poor	—	—	—	44	
C. O.	Good	—	—	—	90	Excellent hospital diet
M. K.	Good	—	—	—	190	Marked fault in absorption of vitamin C
R. R.	Fair	6	1.2	6	10	"Leveled off" at 11.7 per cent
W. F.	Poor	7	1.5	5.5	25	
B. D.	Poor	10	1.8	13	—	
P. T.	Poor	6	2.7	40	25	
M. R.	Good	5	2.9	9	—	Chronic "mucous colitis"; B <sub>1</sub> supplement daily 150 I.U.
R. P.	Poor	6	2.9	8	—	Excretion constant 330 gamma after 1 mg. once daily for 1 month
A. P.	Poor	5	3	16	32	Acute exacerbation, febrile
B. W.	Fair	6	3.4	23	—	Dizziness and weakness attributed to vascular hypertension cleared on 2 mg. thiamin thrice daily 2 weeks
B. M.	Poor	6	3.5	31	0	
H. C.	Fair	8	4.9	26	—	
A. K.	Fair	5	4.4	20	—	
L. H.	Fair	5	4.5	8	—	
T. H.	Fair	6	5	19	—	
C. K.	Fair	7	5.2	21	—	
M. M.	Fair	8	5.5	31	—	
M. S.		5	5.6	25	—	
A. S.	Good	5	5.8	58	—	
F. W.	Fair	5	5.8	24	—	
R. S.	Good	6	6	21	—	
R. C.	Good	5	7.8	11	80	Good hospital diet
A. B.	Good	7	9.9	24	85-130	Good hospital diet
M. W.	Fair	5	10	59	—	
F. G.	Good	4	13.9	50	—	

## DISEASE OF THE GASTROINTESTINAL TRACT

In this group (table 15) the most striking findings were in patients with ulcerative colitis, where the excretions were much lower than would be expected from the diets. This conforms to the results obtained experimentally by Dann and Cowgill<sup>26</sup> who showed that absorption of thiamin in dogs was decreased by 20 to 80 per cent by diarrhea produced with magnesium sulfate.

Of great theoretical interest are the excretions in patients with cirrhosis, referred to above, in whom it appears that, probably because of decreased ability of the liver to phosphorylate thiamin for utilization and storage, the excretion is significantly increased.

R. M. provided an example of the effect of thiamin in non-specific diarrhea, recently discussed by Cheney.<sup>27</sup> A middle-aged, rather nervous woman, she had had a distressing diarrhea for about two years. For the past year she had been treated by a gastroenterologist with the usual bland



TABLE XV  
Patients With Disease of the Gastrointestinal Tract

Patient	Diagnosis	Diet	Resting Gamma/ 24 hr.	Dose mg.	Per cent Ex- creted	Gamma/ 100 ml. Urine	Comment
F. A.	Chronic ulcerative colitis, acute relapse	Fair	0; 0; 5	6	1.5	7	Excretion only 2% after 8 test doses
S. S.	Chronic ulcerative colitis, acute relapse	Fair	0	6	0	0	Excretion only 1% after 4 test doses
V. C.	Amebic colitis	Good	—	6	1.1	3	
L. G.	Chronic ulcerative colitis	Fair	18; 7; 6	3	1.6	10	Later excreted 500-700 gamma per 24 hours on suppl. of 600 I.U. daily
L. D.	Chronic ulcerative colitis	Good	10	6	1.3	8	Excellent hospital diet
D. C.	Celiac disease	Good	80; 105	1.5	15	35	
M. C.	"Spastic colon"	Good	—	5	7.2	13	see below
R. M.	Diarrhea	Poor	—	5	1.3	7	Milk and cream only for months
E. P.	Peptic ulcer	Good	95	5	10	21	Modified ulcer diet
N. R.	Peptic ulcer	Fair	30	4	4.9	26	Gastritis shown by gastroscopy 7 mos. after partial resection for ulcer
R. H.	Gastritis	Poor	—	5	0.6	5	
O. W.	Gastric carcinoma	past month	—	—	—	—	
M. J.	Hematemesis, recurrent; no cause except early cirrhosis found in two laparotomies; neuritis and "beri beri heart" 1 year ago	Good	—	5	5.1	11	Excretion "leveled off" at 15-17% after peak of 25%
		Poor	—	6.6	0.5	13	
M. S.	Cirrhosis; alcoholic; jaundice; neuritis	Poor	—	7.5	0.6	5	Excreted 25% of 10 mg. I.V.
W. B.	Obstructive jaundice	Good	100; 185	7	7.4	35	
A. R.	Obstructive jaundice	Good	75; 110	7	7.9	61	Diet of beans 2 months
M. E.	Cirrhosis, poss. amyloid	Fair	40	5	13	19	"Leveled off" at 19 per cent
M. L.	Obstructive jaundice	Fair	15	5	7.8	37	
	Cirrhosis	Poor	—	6.6	6.0	100	"Leveled off" at 26%, then dropped to 15%

diet, powders, and atropine. She excreted only 1.3 per cent of the test dose. Thiamin chloride was given in a single dose of 5 mg. daily by mouth, and within 10 days she was having one formed stool daily instead of three to five mushy or liquid stools. At this time she excreted 15.4 per cent of the dose. The dose was then reduced to 1 mg. twice a day, and she has since (for three months) remained free of symptoms. An interesting feature was recovery of the ability to take milk, which had formerly caused severe digestive disturbances.

#### LEVEL OF EXCRETION AT WHICH SYMPTOMS MAY APPEAR

Table 16 presents data bearing upon the "level" of thiamin saturation below which symptoms of deficiency may appear. The patients were selected from the groups noted in the previous tables, with a few additions. The criteria of deficiency (aside from subnormal excretions) were: (1) presence of symptoms that are known to result from thiamin deficiency; and (2) definite relief of symptoms following administration of synthetic thiamin in moderate dosage. Since the manifestations of early or mild thiamin deficiency (as well as other deficiencies) are largely subjective, evaluation of improvement is difficult. Most of these patients had had various medications previously without much effect, and it was believed that psychological factors were thereby minimized.

It is seen that symptoms of thiamin deficiency may occur with excretions as high as 4 per cent of the test dose of 0.1 mg. per kg. of body weight. This observation is generally in agreement with the work of Jolliffe et al.<sup>28</sup> who produced symptoms of thiamin deficiency in human subjects within a few days on low-thiamin diets, and found that thiamin continued to be excreted in significant, though decreased amounts. These findings, coupled with the facts that the major portion of vitamin B<sub>1</sub> in the blood is not in the form of free thiamin<sup>30</sup> and that diuresis may greatly increase the excretion, suggest that thiamin is a non-threshold substance. Unfortunately, there are as yet no good data on the relationship of blood thiamin to urinary thiamin.

It must not be supposed that thiamin feeding will bring about clinical improvement in all patients with any or all of the symptoms noted above, even where low excretions are found. Some of our patients with low excretions were not significantly improved in anorexia, sense of ill health, paresthesias, or constipation by thiamin feeding, and in these it must be supposed that the symptoms had causes other than thiamin deficiency, the latter being only an incidental finding.

On the other hand, several patients with symptoms suggestive of thiamin deficiency disease who had normal excretions were not significantly affected by the giving of a supplement. Such a patient was B.M. (table 8).

TABLE XVI  
Levels of Excretion Associated With Symptoms of Deficiency

Patient	Primary Diagnosis	Per cent of Test Dose Excreted	Therapeutic Dose	Symptoms Improved
T. E.	"Scalenus anticus syndrome"	0	1 mg. thrice daily	Anorexia, fatigability
N. J.	Alcoholic neuritis	0.2	3 mg. thrice daily	Anorexia, pain, weakness, paresthesia
R. H.	Alcoholic neuritis	0.3	3 mg. thrice daily	Anorexia, pain, weakness
F. T.	Multiple sclerosis	0.5	10 mg. daily (I.M.)	Anorexia, weakness, acroparesthesias
C. G.	CNS lues	0.7	1 mg. thrice daily	Formications, lassitude, constipation
C. A.	Alcoholic neuritis	0.8	3 mg. thrice daily	Anorexia, pain, paresthesias, weakness
A. H.	Psychoneurosis	1.2	5 mg. I.M. every 2 days	Acroparesthesias, anorexia, weakness
R. M.	Chronic diarrhea	1.3	5 mg. once daily	Diarrhea, sense of ill health
E. W.	Hypertensive cardiovascular disease	1.4	10 mg. twice daily	Weakness, anorexia
F. D.	"Post influenzal" neuritis	1.5	10 mg. thrice daily	Pain, weakness
S. C.	Malnutrition, anemia	1.6	3 mg. thrice daily	Anorexia, weakness, weight loss
A. F.	CNS lues	1.7	1 mg. thrice daily	Anorexia, facial neuralgia, asthenia
C. G.	Tic douloureux	2.0	3 mg. thrice daily	Anorexia, underweight. Sense of ill health
P. O.	CNS lues	2.0	1 mg. thrice daily	Anorexia, weakness, underweight
B. C.	Bronchopneumonia, poor convalescence	2.0	5 mg. once daily	Anorexia, weakness
G. C.	CNS lues	2.1	1 mg. thrice daily	Fatigability, anorexia
M. R.	Tachycardia unknown cause; malnutrition	2.6	0.6 mg. thrice daily	Anorexia, palpitation, general sense of ill health
C. S.	CNS lues	3.3	2 mg. thrice daily	Anorexia, paresthesias; sense of ill health
B. W.	Hypertension, arthritis	3.4	2 mg. thrice daily	Weakness, dizziness
A. C.	CNS lues	3.4	2 mg. thrice daily	Sciatic pain, fatigability
L. R.	Neuritis arm and leg	3.6	2 mg. thrice daily	Pain, anorexia, underweight, lassitude
K. H.	Chronic alcoholic neuritis	3.6	0.6 mg. thrice daily	Paresthesias, weakness
M. P.	Malnutrition	4.6	0.6 mg. thrice daily	Anorexia, underweight, lassitude
W. C.	Tic douloureux	4.8	3 mg. thrice daily	Anorexia, fatigability

## SUMMARY AND CONCLUSIONS

A modification of the thiochrome reaction of Jansen provides an easy, rapid, and accurate method for the chemical assay of thiamin (vitamin B<sub>1</sub>) in urine.

Subjects taking a diet known to be adequate in thiamin excrete in the urine from 100 to 300 micrograms daily. Of a standard test dose of 0.1 mg. per kilogram given by mouth 8 to 10 per cent is excreted, most of the excess being found in the first five hours.

The per cent excretion is roughly inversely proportional to the size of the dose given by mouth, and roughly directly proportional to the size of the dose given parenterally. The efficiency of utilization of thiamin supplements depends in part upon the degrees of absorption and excretion, large doses orally being incompletely absorbed and large doses parenterally being rapidly excreted, so that small frequent doses are most efficiently utilized.

The excretion reflects the intake with great sensitivity, even very slight degrees of subsaturation being readily detected. The extent of deficiency may be estimated by determining the number of test doses required for the excretion to rise to normal. In patients with severe thiamin deficiency disease, presumably markedly undersaturated, the total amount required for the excretion to become normal was tentatively estimated at about 100 mg.

Evidence is presented that thiamin is a non-threshold substance. Diuresis may wash out a considerable amount, thus contributing to the development of deficiency.

Data indicating that in diffuse liver disease the excretion may be much higher than normal are interpreted as evidence that the ability to phosphorylate thiamin for utilization and storage is impaired.

Moderate deficiencies were found in patients with thyrotoxicosis despite diets containing fair amounts of "protective foods." This may be explained by the increase in the metabolic rate and the consequent increase in the thiamin requirement, left uncompensated by the addition to the diet of vitamin-poor carbohydrate foods.

In several patients with "neuritis" of uncertain cause significant deficiencies were found. Some of these experienced definite relief after thiamin feeding, indicating that thiamin deficiency played a part in the etiology, although classical thiamin deficiency disease was not present.

Fifty per cent of patients with multiple sclerosis were markedly subsaturated, and 29 per cent had definite symptomatic improvement after administration of thiamin by mouth. It is thought that the deficiency is secondary, there being no evidence that the primary disease was influenced by the treatment.

Deficiencies were frequently found in patients with dorsolateral sclerosis and miscellaneous diseases of the central nervous system.

Eighty per cent of patients with central nervous system syphilis were found to be undersaturated with thiamin. Of these, 58 per cent had definite

improvement in general health or neurological symptoms or both following administration of pure thiamin.

A preliminary report is presented of the effect of thiamin in tic douloureux. There appears to be a definite indication for its use as a therapeutic measure. It is probable that long-continued administration of the vitamin is necessary in some patients before improvement will begin.

Severe deficiencies of thiamin were found in patients with diarrhea, apparently because of inadequate absorption. Thiamin feeding was found to be curative in a patient with non-specific diarrhea, who also recovered from an idiosyncrasy to milk.

Thiamin deficiency is very frequently found in mild degree in patients with chronic disease of various types, and may produce symptoms which are attributed to the primary disease, or to "functional" disorders. Because of the absence of the classical picture of deficiency disease, these can be diagnosed only by the therapeutic test. By estimating the urinary excretion, asymptomatic deficiencies may be readily discovered, and the therapeutic test may be placed upon a sounder basis in diagnosis of deficiencies associated with symptoms.

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# VITAMIN DEFICIENCIES IN GASTROINTESTINAL DISEASE \*

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No field of internal medicine is attracting more attention nor yielding a more rapid accumulation of important information than the study of the avitaminoses. Until very recently the term vitamin deficiency disease has been restricted to a small group of conditions representing maximal degrees of deprivation including such entities as rickets, scurvy, pellagra, beri beri, sprue, and certain macrocytic anemias. The belief has been widespread therefore that vitamin deficiencies are uncommon if not actually rare.

The changing perspective of the present is directly traceable to the chemical identification and synthesis of many of these specific food factors. This has permitted great broadening of the field of research. Investigation of the pathology of avitaminosis has been supplemented by study of the physiology of the vitamins particularly with reference to their function in cellular metabolism. Chemical and physical tests have been devised which permit quantitative measurements of vitamin concentration in biological materials; and availability of the pure synthetic vitamins has permitted confirmation by the therapeutic test. Finally the hospital ward has been linked to the nutrition laboratory. The fruitfulness of this field is attested by the increasing volume of clinical literature which is associating a great variety of disease conditions with a varied and at times highly significant vitamin deficit.

The number of vitamins known to be required for human nutrition has increased as research has progressed and it is almost certain that others will be added in the future. The vitamins today known to be required by man are A, thiamin, riboflavin, nicotinic acid (amide), B<sub>6</sub>, C, D, K and possibly E.

## PATHOLOGY OF VITAMIN DEFICIENCY

Present concepts of the pathology of the avitaminoses are, to a large extent, based upon studies of experimental animals subjected to deficient diets. Certain of the changes found in these animals have been observed in man,<sup>1</sup> others have not. The field is new, however, and requires much additional study. The following discussion of the anatomic changes accompanying avitaminoses is based upon the experimental pathology and such confirmatory observations in man as are available. Necessarily it is incomplete.

The maintenance of specialized epithelial structures has been shown to be the primary function of vitamin A. Atrophy followed by metaplasia and

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differentiation into stratified squamous epithelium results from deprivation of this vitamin. These changes occur in the cornea, the conjunctiva, the parocular glands, and the respiratory tract. They have not been demonstrated to occur in the gastrointestinal tract of man. There are characteristic manifestations in the skin. The most striking of these are excessive dryness and scaliness, and the development of keratotic plugs in the hair follicles, the so-called hyperkeratosis follicularis. There is cessation of bone growth due to failure of cartilage differentiation. Osteoid tissue is scanty and both bone and cartilage become densely calcified. The enamel organ of the teeth is affected and imperfect enamel is produced.

Thiamin, vitamin B<sub>1</sub>, or the antineuritic vitamin is intimately associated with beri beri, and with certain forms of peripheral neuritis. It has not been proved, however, that deficiency of this vitamin *per se* is responsible for the characteristic pathology. Recently it has been shown that administration of beta carotene or percomorph oil with riboflavin removes all evidence of peripheral nerve pathology in thiamin deficient chicks, and conversely, that neuropathologic changes seldom occur in rats maintained on a diet deficient in thiamin but adequate in other respects.<sup>2</sup> This suggests that the myelin degeneration in human beri beri depends upon factors other than a simple lack of the antineuritic vitamin. Chemical evidence indicates that polyneuritis is a disease characterized by a general disturbance of carbohydrate metabolism, rather than one primarily producing lesions of the nervous system.<sup>3</sup> Advanced grades of thiamin deficiency, however, are accompanied by extensive changes. There is degeneration of the myelin sheaths of peripheral nerves, and vacuolation and liquefaction necrosis of the ganglion cells of the mesencephalon, metencephalon, and the anterior horn cells of the spinal cord.

Our knowledge of the pathology of riboflavin deficiency is almost certainly incomplete. Recently, however, certain definite lesions have been recognized in man.<sup>4, 5</sup> The lips become reddened and shiny with maceration and fissuring at the angles of the mouth. Seborrheic accumulations develop in the naso-labial fold. The tongue becomes clean and purplish red or magenta in color and presents flattened mushroom-shaped papillae. Capillary ingrowth into the cornea occurs. There is interstitial infiltration with exudate, and the development of diffuse or patchy superficial and interstitial corneal opacities. Experimental animals and birds maintained on a riboflavin-deficient diet, exhibit specific lesions. Myelin changes, especially in the main peripheral nerve trunks occur in chicks.<sup>6</sup> A characteristic dermatitis is produced in rats.<sup>7</sup> Excess fat is found in the liver of birds.<sup>8</sup> Dogs present a yellow mottling of the liver and degenerative changes in the central nervous system.<sup>9</sup>

The demonstration that nicotinic acid was curative for experimental "black tongue" in dogs<sup>10</sup> was immediately followed by its application to the problem of human pellagra for which it likewise was found to be curative.<sup>11, 12, 13, 14</sup> Nicotinic acid deficiency therefore, is directly linked to acute



glossitis, stomatitis and enteritis. Characteristic changes occur in the skin especially in those areas exposed to sunlight. Acute dermatitis appears first, followed by pigmentation and atrophy which leaves the skin thin and parchment-like. Similar changes although usually less intense may occur in the peri anal region, the scrotum, vulva, and vagina.

The pathology of vitamin B<sub>6</sub> deficiency has not been established as yet.

Vitamin C, ascorbic acid, has been extensively studied. Lack of this vitamin leads to inability of supporting tissues to produce and to maintain normal inter-cellular matrix. This results in weakening of vascular walls, increased capillary fragility and consequent extravasation of blood. It likewise produces abnormalities of tooth structure in young animals. Odontoblasts are replaced by osteoblasts, bone is produced instead of dentine, and the dental pulp undergoes fibroid degeneration.

The rôle of vitamin D deficiency in the production of pathologic changes in the growing bones of young animals is well proved. A variety of dental defects are demonstrable in experimental animals maintained on a rachitic diet. The teeth erupt late. They are irregularly set. The enamel is of poor quality. And the jaw bone is spongy.

It is probable that it affects human dentition as well. There is clinical evidence that vitamin D plays an important rôle in tooth formation, and the maintenance of normal tooth structure in man. This probability is supported by the demonstration that the mineral content of the teeth is not completely fixed, but subject to constant mobilization and replacement.<sup>15</sup>

The relationship of vitamin E deficiency to human disease is based mainly upon the therapeutic value of this substance in the control of certain cases of habitual abortion and muscular dystrophy. Lack of this vitamin impairs fertility of experimental animals by interference with placental function in the female, and with spermatogenesis in the male.<sup>16</sup>

A second antihemorrhagic factor, vitamin K, has recently been recognized. It is an oil soluble substance which requires the presence of bile salts for absorption from the intestine. This vitamin plays an essential although indirect rôle in the blood clotting mechanism by ensuring a normal supply of pro-thrombin, provided the liver is functionally active. Deficiency of this vitamin by interference with blood clot formation is an important factor in hemorrhage which may be spontaneous and which may be both dangerous and prolonged.

#### ENERGY METABOLISM AND THE VITAMINS

Until very recently the avitaminoses have been considered only in terms of anatomic pathology. The unfolding of the chemical structure of the vitamins and their synthesis in pure form have opened a new field of research in biochemistry and physiology. Evidence already available demonstrates that the vitamins play an essential rôle in the metabolism of all living cells.<sup>17</sup> Lacking these substances cellular metabolism is impaired and func-

tion altered. Implicit in these facts are possibilities of enormous potential importance in clinical medicine. Furthermore the pathology of vitamin deficiencies is placed in a new perspective. The characteristic lesions of single avitaminoses must be regarded as the anatomic response to extreme deficiency by the most vulnerable tissue, rather than as a complete picture of the effects of the particular deficiency.

Szent-Gyorgyi<sup>18</sup> has stated that whenever nature provides a system offering two potential energy levels and the possibility of energy release, life appears, causes the system to drop to its lower energy level, and utilizes the energy liberated for its own purposes. The sources of this energy for life are to be found in the intra-cellular oxidation and reduction systems of the body. They are two-fold. The union of two atoms of hydrogen with one of oxygen yields 68 calories. Sugar must first be phosphorylated in the process of yielding its energy, and additional energy is released in the formation of phosphoric acid esters.

Liberation of energy, however, must be gradual rather than sudden or explosive which would be destructive to the cell. This is accomplished by three sets of compounds: enzymes (dehydrogenases and phosphatases) which detach hydrogen and phosphoric acid from the food molecule; acceptors which can receive and carry hydrogen, phosphoric acid, and electrons (co-enzymes, phosphoric acid esters, cytochromes); and lastly enzymes that activate substances to accept hydrogen, phosphoric acid, and electrons (oxidases, metal proteids). Furthermore, the transport and shift of hydrogen, phosphoric acid, and electrons require the presence of other enzymes and coenzymes such as mutases, carboxylases, and cocarboxylases.

Thiamin, riboflavin, and nicotinic acid amide have been shown to be the chemically active or prosthetic group in many of the enzymes required by the mammalian body. The chemical structure of B<sub>6</sub>, E, and K makes it highly probable that they perform a like function. Ascorbic acid by virtue of its capacity for reversible oxidation and reduction is chemically capable of acting as a hydrogen carrier.

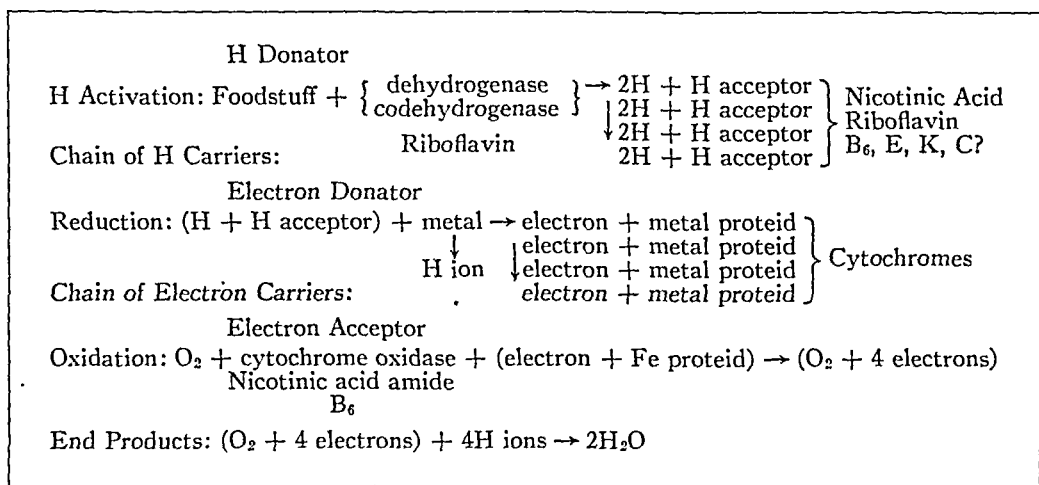
The fundamental rôle of the vitamins in the processes of intracellular metabolism may be emphasized by schematic presentation. This is diagrammed in charts 1 and 2. The actual processes of energy release, however, are infinitely more complicated and many of the intermediate steps are still unknown.

The foodstuff molecule, or hydrogen donator, on activation by dehydrogenase yields two atoms of hydrogen to the coenzyme, codehydrogenase, an integral part of which is frequently riboflavin. The hydrogen is then handed on to the chains of hydrogen acceptors through which it passes. Nicotinic acid amide, riboflavin, B<sub>6</sub>, E, and K all can function as hydrogen acceptors. Although ascorbic acid is chemically able to act in this way, it has not been proved to do so in the animal body.

At the end of the chain the hydrogen-hydrogen-acceptor complex is re-

duced by a metal yielding a hydrogen ion and an electron. The electron in its turn is passed along a chain of electron carriers, the metal proteids or cytochromes. Finally cytochrome A is oxidized by cytochrome oxidase, integral constituents of which are nicotinic acid amide and  $B_6$ . Oxygen enters into this reaction taking up electrons previously given off by hydrogen. After receipt of the electrons, the oxygen reacts with hydrogen ions to form water. The available energy of the hydrogen of the foodstuff is thus progressively liberated by the passage through the chain of hydrogen carriers, and finally by giving up its electron to the electron carrier. The rôle of oxygen is limited to that of an electron acceptor.

CHART I  
Biological Oxidation to  $H_2O$   
68 Calories

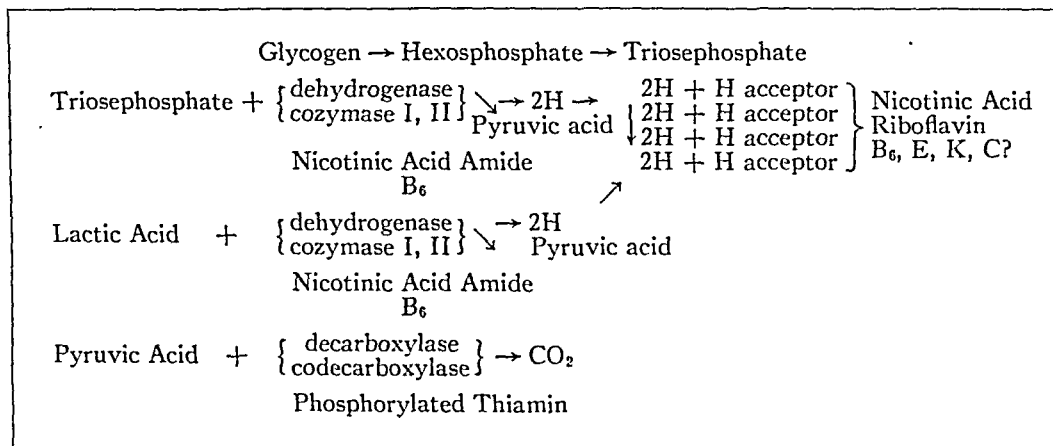


The carbon dioxide formed in the body is not a product of oxidation but is split out of organic acids. It is probable that it is produced by decarboxylation of pyruvic acid, an intermediate product of carbohydrate and fat metabolism. Here again the joint action of enzymes and coenzymes is required. Nicotinic acid, vitamin  $B_6$ , and thiamin are essential constituents of certain of these coenzymes.

Chart 2 presents schematically the oxidation of carbohydrate to carbon dioxide. Triosephosphate on activation by a dehydrogenase gives up hydrogen to cozymase. This coenzyme contains nicotinic acid and  $B_6$ . Pyruvic acid is formed by this reaction. Lactic acid, an intermediate product in the metabolism of muscle, similarly yields pyruvic acid and hydrogen. The hydrogen for these reactions is passed through the chain of carriers, ultimately to form water as indicated in chart 1. Pyruvic acid, however, in the presence of the enzyme decarboxylase, and the coenzyme codecarboxylase of which phosphorylated thiamin is an integral part, yields acetaldehyde and carbon dioxide.

Vitamin D although apparently playing no direct rôle in these oxidation-reduction reactions plays an important part in cellular energy metabolism by its control of phosphorus availability. The phosphate ion is an essential constituent of many enzymes.

CHART II  
Biological Oxidation to  $\text{CO}_2$



#### PHYSIOLOGIC DISTURBANCES IN VITAMIN DEFICIENCY

In view of the fundamental importance of the vitamins in the metabolism of individual cells a variety of physiologic disturbances must accompany avitaminosis. It is to be anticipated that more than one function will be disturbed by deficiency of a single vitamin and that these disturbances will find expression in different physiologic systems within the body. Actually, available evidence confirms this.

In vitamin A deficiency the secretory function of the skin is impaired. The regeneration of the visual purple of the retina is affected and hemeralopia, or night-blindness, results. Reduction of the urea and creatinine clearances with improvement following correction of the avitaminosis has been reported.<sup>19</sup>

Deficiency of thiamin has been related to a variety of physiologic disturbances. Peters and his associates have demonstrated that in the absence of thiamin the breakdown of carbohydrate is impaired at the pyruvic acid level and that this substance accumulates in blood.<sup>20</sup> As the deficiency develops there is a progressive diminution in carbohydrate tolerance and the development of hyperglycemia which precedes the nervous disturbances.<sup>21</sup> The circulatory system becomes embarrassed. Tachycardia, cardiac enlargement, edema, evidence of cardiac failure and alteration in the electrocardiogram, chiefly T-wave changes, occur.<sup>22</sup> Anorexia appears early, and may respond with extraordinary rapidity, even within 24 hours, to adequate dosage. A variety of gastrointestinal abnormalities including achlorhydria, hypomotility, and atonicity have been attributed to lack of thiamin. Final

proof, however, is lacking. Similarly a variety of nervous and emotional disturbances exclusive of the characteristic neuritis, best described as the syndrome of neurasthenia, have been ascribed to thiamin deficiency.

As yet no demonstrable physiologic disturbances in man have been attributed to lack of riboflavin.

Nicotinic acid, however, appears to exert an immediate effect upon the concentration of cozymase in the blood. Low values corrected by the administration of nicotinic acid have been observed both in pellagra and in diabetes mellitus.<sup>23</sup> Certain types of psychosis occurring in the absence of the characteristic phenomena of pellagra likewise appear to depend upon nicotinic acid deficiency.<sup>24</sup>

Vitamin B<sub>6</sub> deficiency appears to be responsible for certain of the muscular and neurologic symptoms of pellagra which do not respond to nicotinic acid or thiamin therapy.<sup>25</sup>

Ascorbic acid is intimately related to the utilization of iron. The anemia of scurvy, though refractory to iron and liver extract, responds to the exhibition of ascorbic acid by marked reticulocytosis and rapid blood regeneration.<sup>26, 27</sup> This vitamin is said to exert an anti-goiterogenic effect by conserving iodine in the body.<sup>28</sup> It is also fairly well established that vitamin C plays some rôle in immunity through its effect upon the complement activity of the serum,<sup>29</sup> and the process of agglutination.<sup>30</sup>

Vitamin D functions to insure maximal utilization of calcium and phosphorus both by reducing excretion and by increasing absorption. The relationship of deficiency of this factor to certain types of tetany is well known. It is probable that the alimentary glycemia, the lowered oxygen consumption, and the muscular weakness of rickets may all be explained by the disturbed phosphate metabolism.

In view of the varied effects of vitamin deprivation upon normal physiology it is not unexpected that while avitaminosis remains at the level of disturbed physiology, the resulting clinical phenomena will be diverse, atypical of any definite disease entity, and accompanied by few if any physical signs. Certain accompanying symptoms, however, are suggestive. In the presence of more advanced deficiency disease when anatomic changes have appeared diagnosis is often simple. The major symptoms and signs of vitamin deficiency disease are presented in table 1.

What evidence is there that avitaminosis is other than a medical curiosity? The suspicion is growing that the average American dietary is at least sub-optimal. The average protein intake is said to have decreased from 100 grams to from 50 to 60 grams per diem in a generation.<sup>31</sup>

Thirty per cent of this is obtained from wheat, a protein which is biologically incomplete. Approximately one-fifth of the total caloric value of the diet is derived from sugar, and four-fifths from foods which have lost much of their vitamin content in various refining processes.

Nutritional surveys indicate that defective diets are demonstrable only in the low income groups.<sup>32</sup> The Council on Pharmacy and Chemistry and the

Council on Foods of the American Medical Association have stated that "—with the exception of pellagra and a possible vitamin B<sub>1</sub> deficiency there is no evidence of a noteworthy prevalence in this country of conditions in adults that might properly be ascribed to a lack of one or more vitamins." <sup>33</sup> They suggest, however, that the optimal diet should contain more vitamin A, thiamin, ascorbic acid and in certain areas more riboflavin and nicotinic acid. It is probable that vitamin D should also be included in this list.

Evaluation of dietary adequacy even for the healthy individual is subject to error. The actual daily requirements for the particular vitamins are unknown. The recommended amounts are based upon assumed minima to which an assumed amount is added as a factor of safety. These recom-

TABLE I  
Symptoms and Signs of Vitamin Deficiency

Vitamin	Symptoms	Signs
A	Night blindness	{ Dry scaly skin Follicular hyperkeratosis Bitots spots
Thiamin B <sub>1</sub>	{ Anorexia Peripheral neuritis Cardiac failure	{ Muscle tenderness Hyperreflexia—areflexia Diminished vibratory sense Tachycardia
Riboflavin	?	{ Cheilosis Seborrheic dermatitis }? Glossitis Keratitis
Nicotinic Acid	{ Painful mouth and tongue Diarrhea, dermatitis Psychosis, stupor	{ Inflamed, denuded tongue Dermatitis, symmetrical, scrotal, vulval, peri anal
B <sub>6</sub>	Weakness, insomnia, nervousness (?)	?
Ascorbic Acid C	{ Bleeding Pain	{ Petechiae Spontaneous hemorrhage
D	{ Rickets Weakness	{ Cessation of bone growth Disturbed Ca -P metabolism Osteoporosis ?
E	Habitual abortion ?	Muscular dystrophy ?
K	Bleeding	{ Petechiae Spontaneous hemorrhage

mended amounts from time to time are being increased. Thus from 40 to 60 milligrams of ascorbic acid have been considered an adequate daily allowance. <sup>34</sup> Recently, however, Ralli <sup>35</sup> and her coworkers have found that tissue saturation can be maintained only on a daily intake of at least 100 milligrams. Nutritional surveys based on diet evaluation are estimated from average values of "as purchased" foods and not on the "as served" foods. They do not consider sufficiently the actual individual intake nor the methods of preparation which may produce considerable loss or destruction of the natural vitamin content. Thus cooking with soda, cooking in excess water which is discarded, home canning, pasteurization of milk, and certain methods of preparing meats result in large loss or even complete destruction of at least ascorbic acid and thiamin. There is therefore perhaps a greater weight of

evidence to indicate that the average diet is deficient than that it is adequate. The comparative rarity of gross deficiency disease is not a valid argument that deficiencies at the physiologic level do not exist.

The development of technics for vitamin determination in blood and urine is progressing rapidly. Certain of these are relatively dependable, particularly those for vitamin A, carotene, ascorbic acid, and vitamin K.

Application of these methods to clinical investigation is indicating a far higher incidence of vitamin deficiencies than has been suspected hitherto. The physiologic states of pregnancy and lactation are accompanied by increased requirements for mineral salts and for vitamins. Continued fever produces an increased utilization or loss of ascorbic acid and a raised requirement in comparison with the healthy individual. Deficiencies of this vitamin have been observed in a variety of medical conditions and in postoperative surgical cases. In the evaluation of reports of this type it is important to keep in mind the probability that when one deficiency is demonstrable others are almost certainly present.

Vitamin deficiency states are becoming increasingly important in disorders of the gastrointestinal tract. They may occur from various causes. Conditions such as sprue and extensive regional enteritis are accompanied by defective absorption. Multiple intestinal fistulae and gastro-colic and gastro-jejuno-colic fistula by short-circuiting the intestinal contents prevent normal utilization of diet. Obstructive jaundice or biliary fistula, by exclusion of bile salts from the intestine, condition both vitamin K and vitamin A deficiencies. Intrinsic disease of the liver may likewise be an important factor in the etiology of avitaminosis. Hypermotile diarrheas, in theory at least, also contribute to the development of deficiency by too rapid elimination of the food substrate. The deficiency states occurring in these conditions are termed secondary or conditioned.

The designation primary is reserved for those deficiencies which develop as the result of defective diet. These are not uncommon. They may be exceedingly important. So-called gastrointestinal diets are traditionally oversupplied with starches and sugars. The fruits and green vegetables are proportionally diminished. Functional disorders of the gastrointestinal tract are frequently related to insufficient supplies of the vitamin B complex.<sup>36</sup> In such circumstances restriction to certain of the therapeutic diets will have an additive effect and may precipitate serious deficiency disease. Clinical observations indicate that these deficiency states are accompanied by changes in the small intestine analogous to those which occur in sprue,<sup>37, 38</sup> a condition known to be characterized by impaired absorption. In consequence a vicious ascending spiral may be produced.

We have previously reported the occurrence and importance of mixed deficiency states in chronic ulcerative colitis.<sup>39, 40</sup> More recently we have discussed the value of quantitative estimations of blood vitamin A, carotene, ascorbic acid, and prothrombin time.<sup>41</sup> These studies have been continued with particular reference to cases of peptic ulcer and chronic ulcerative colitis

under treatment in the hospital. The detailed data will be presented subsequently.

Determination of the vitamin A, carotene, and ascorbic acid content of the fasting blood have been made on 51 cases of peptic ulcer on admission and at discharge after standard ulcer therapy.

The admission values for these vitamins were definitely below those of the normal controls and the difference is statistically significant. The discharge values are likewise below those of the controls and the differences are also statistically significant. The limited rise of the mean ascorbic acid value under treatment appears primarily to be due to lack of adequate vitamin C in the diet. However, there is evidence to suggest that defective absorption or utilization plays some part.

TABLE II

## Vitamin A

	Normal Controls	Ulcer, Initial	Ulcer, Final	Ulcerative Colitis, Initial
Number of cases	39	48	49	61
Mean	2.06 LBU*	1.5 LBU	1.4 LBU	1.46 LBU
Times probable error of difference		9×	9×	7×

\* Lovibond blue units per 100 c.c.

## Carotene

	Normal Controls	Ulcer, Initial	Ulcer, Final	Ulcerative Colitis, Initial
Number of cases	38	50	49	61
Mean	0.75 LYU*	0.63 LYU	0.49 LYU	0.75 LYU
Times probable error of difference		2.4×	6.5×	0

\* Lovibond yellow units per 100 c.c.

## Ascorbic Acid

	Normal Controls	Ulcer, Initial	Ulcer, Final	Ulcerative Colitis, Initial
Number of cases	42	51	51	63
Mean	0.76 mg.*	0.5 mg.	0.61 mg.	0.64 mg.
Times probable error of difference		6×	3×	2.5×

\* Milligrams per 100 c.c.

Comparison of the vitamin A values before and after treatment reveals an actual fall of the mean. It is impossible to explain this finding on the grounds of dietary inadequacy. The diet supplied optimal amounts of vitamin A at all times according to present standards. This strongly suggests imperfect absorption. The greater fall of the mean carotene value is not unexpected in view of the limited amounts of green vegetables supplied by the diets. The lack of correlation between the blood A and carotene levels is in keeping with the findings of others.

Similar studies were made of 63 cases of chronic ulcerative colitis when they first came under our observation. The mean blood A and ascorbic acid values are below those of the control group. The differences between the



groups are statistically significant. The mean carotene values, however, were identical.

The disproportion between the levels of blood A and carotene in the controls and in the colitis cases suggests a metabolic defect in the translation of the provitamin carotene to vitamin A. The low ascorbic acid values observed in many of these patients were due to grossly deficient diets, and frequently were associated with severe bleeding from the inflamed colon. Defective absorption, however, appeared to be a factor in at least some of the vitamin A deficiencies. Failure to respond to large oral doses of this vitamin in the form of fish liver oil was common. However, when cod liver oil was administered by inunction prompt and satisfactory rise of the blood A was usually obtained.

The prothrombin time of Quick <sup>42</sup> has been used to determine the vitamin K status in 73 miscellaneous non-jaundiced patients. Twenty-two of these have had elevated prothrombin times. The detailed data will be presented subsequently.

TABLE III  
Vitamin K Deficiency without Jaundice

Ulcerative colitis . . . . .	18 cases
Regional enteritis . . . . .	2 cases
Tropical sprue . . . . .	1 case
Banti's disease . . . . .	1 case

In certain instances this deficiency has been associated with a grossly defective diet and has responded to dietary measures alone. The case of Banti's disease developed a marked elevation of prothrombin time in the course of starvation and limited diet therapy for gastric hemorrhage. It promptly fell to the normal level on resumption of more liberal diet. Similarly the patient with sprue developed a considerably elevated prothrombin time in the postoperative period following surgical intervention for intestinal obstruction. Again return to adequate diet was followed by fall of the prothrombin time to normal. Likewise several of the cases of ulcerative colitis fall into this category.

Our observations indicate, therefore, that jaundice is not a necessary concomitant of vitamin K deficiency and that this complication may constitute part of a mixed vitamin deficiency syndrome. In view of the conditions in which it has been observed the precipitating factors appear to be a chronic disease of the gastrointestinal tract to which is added the effect of starvation, defective diet, poor absorption, or a hypothetical qualitative or quantitative defect of bile secretion.

It is axiomatic that recognition of a vitamin deficiency calls for immediate treatment. This may be accomplished by diet alone, or by diet and supplemental vitamin therapy. In the presence of acute deficiency the latter regime should be used. If the indications for specific vitamin administration exist ample dosage should be used as indicated in table 4.

However, too much dependence must not be placed upon the use of the

purified vitamins, to the neglect of careful dietetics. It is still impossible to keep an experimental animal alive on a vitamin-free food mixture to which have been added ample amounts of all the presently known purified vitamins. Diet still remains the major weapon to combat deficiency disease. It is often advisable to supplement it with crude sources such as Brewer's yeast or unrefined liver extract in large amounts. The purified vitamins should be used as an additional form of therapy to meet special and usually temporary indications.

TABLE IV  
Vitamin Therapeutic Dosage

Vitamin A	35,000–100,000	U.S.P. Units per day
Thiamin chloride	20–30	mg. per day
Riboflavin	5	mg. per day
Nicotinic acid	250–500	mg. per day
Vitamin B <sub>6</sub>	50	mg. per day
Ascorbic acid	500– 1,000	mg. per day
Vitamin D	1,200– 60,000	U.S.P. Units per day
Vitamin K	1	mg. per day

### SUMMARY

The concept of vitamin deficiency disease is being rapidly and radically revised as the result of research in biochemistry. Various of the vitamins have been shown to be the active or prosthetic fractions of enzymes which are essential for the breakdown of foodstuff in intracellular metabolism. They have likewise been shown to have chemical structures which permit them to function in the transfer of hydrogen and phosphorus by which the energy of food is progressively liberated for the use of the individual cell. As this mechanism has been uncovered a variety of metabolic and physiologic disturbances have been associated with the avitaminoses. These are directly traceable to interference with cellular oxidation-reduction systems.

This advance in biochemical knowledge places the problem of the vitamin deficiencies in a new perspective. It is immediately apparent that a vitamin deficiency may exist at two levels. The first is the level of disturbed physiology accompanying the early stages of interference with the chemical processes of the cells. Symptoms may be produced and certain disturbances of normal body chemistry may be demonstrable. Physical signs which depend upon structural alteration, will be absent. However, when the deficiency becomes more intense or of longer duration the level of anatomic change is reached and the classic signs of deficiency disease become evident. Such a concept reconciles the apparently opposed views of those who suspect that vitamin deficiencies are more prevalent than are generally believed, and the view that they are absent because gross deficiency disease is rare.

The function of the stomach and intestinal tract with the accessory organs in the digestion and absorption of food place this system in a position of great importance with respect to the etiology of vitamin deficiencies. Any pathologic condition which interferes with normal food intake, normal di-

gestion, normal absorption of the products of digestion, and normal utilization of these products by the liver, may produce secondary or conditioned avitaminoses.

Primary deficiencies due to defective diet are probably not rare. Many of the dietary regimes in vogue for the treatment of diseases of this system are open to grave suspicion. Our observations of the levels of blood vitamin A, carotene, ascorbic acid, and prothrombin time, demonstrate that diets widely used in the treatment of peptic ulcer and ulcerative colitis are not adequate to maintain normal nutrition.

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# THE RELATION BETWEEN CLINICAL EDEMA AND THE EXCRETION OF AN ANTIDIURETIC SUBSTANCE IN THE URINE\*

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STARLING's hypothesis relating the exchange of fluid between the capillaries and the interstitial body fluids to a balance between hydrostatic pressure within the capillaries and osmotic pressure of the plasma proteins, permits prediction of some conditions under which edema will be found. Moore and Van Slyke<sup>1</sup> found that in adults with Bright's disease when the plasma albumin level fell below 2.5 grams per 100 c.c. edema almost invariably occurred and could not be controlled by salt restriction alone. Farr and Van Slyke<sup>2</sup> found that in similar circumstances the plasma albumin of children averaged 1.2 grams per 100 c.c. Direct measurements of colloidal osmotic pressures in the sera of these patients by Bourdillon<sup>3</sup> showed the pressures to be in the range expected from the plasma protein concentrations. It may be accepted as established by both physiological experiments and clinical observation that diminution of colloidal osmotic pressure in the plasma is an important factor in producing edema, and that the albumin is the plasma constituent of most importance in maintaining the pressure.<sup>4</sup>

However, clinical edema is not infrequently encountered which cannot be explained on this basis. The edema in acute nephritis frequently is not associated with hypoproteinemia, and there may be no evidence of increase of hydrostatic pressure within the capillaries. Likewise in edema regularly recurring during the menstrual cycle, and in certain endocrine diseases as Cushing's syndrome, the observed variations in extracellular fluid volume cannot be explained on the basis of Starling's theory. Fluctuating edema in patients with the nephrotic syndrome occurs not infrequently on a very low salt intake without associated changes in the level of the plasma proteins.

It appears that at least one factor other than plasma protein content and hydrostatic pressure is concerned with edema formation in patients on limited salt intakes. We have, in this clinic for a number of years, called this the "X-factor" in edema formation, but no suitable laboratory means of detecting the presence or absence of this factor have previously been available.

In 1937 Gilman and Goodman<sup>5</sup> reported that the urine of dehydrated rats showed an antidiuretic activity roughly proportional to the severity of dehydration when tested by the rat assay method of Burn.<sup>6</sup> We have applied their method with slight modifications in the study of the presence or

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absence of an antidiuretic factor in the urine of patients and sought to correlate the presence of this factor with the presence of edema in patients.

### METHODS

A 24-hour urine specimen was collected in a clean, sterile bottle and acidified with 2 per cent acetic acid. The entire specimen was placed in cellophane tubes of about 2 centimeters in diameter and about 1 meter in length and suspended in the draft of electric fans. This simple and rapid method for concentration used by Van Slyke, Hastings, Hiller and Sendroy<sup>7</sup> has been refined recently by Thalhimer.<sup>8</sup> The urine was concentrated to an approximate volume of 80 c.c. and then dialyzed. Dialysis was carried out by placing an ordinary glass marble in the cellophane tube containing the concentrated urine, tying off tightly the open end to form a waterproof sack, cutting off the excess cellophane tubing, and placing inside a glass tube 5 centimeters in diameter and 30 centimeters in length. Through this tube a constant stream of tap water flowed while the tube was slowly oscillated through a 30 degree angle longitudinally by a shaking apparatus. Oscillating dialysis was continued for 6 to 8 hours to insure complete removal of urea and salts. The dialyzed and concentrated 24-hour urine specimen was then made up to a volume of 100 c.c.; thereby, each 1 c.c. represented the amount of urine excreted in 15 minutes and this amount was used as the standard bioassay dose.

Each bioassay employed 20 rats, two in each of ten cages after an overnight fast. At 9 a.m. each rat was given 2.5 per cent of its body weight in water by gavage and at 11:30 a.m. 5 per cent of its body weight in water by gavage followed by 1 c.c. of the dialyzed concentrate intraperitoneally. The volume of urine excreted by each cage of rats was then measured at 15-minute intervals starting at the time the intraperitoneal injection had been made. Observations were discontinued when the urine volume of each cage equalled 2.5 per cent of the sum of the initial body weights of the rats therein. The period of time required to attain this volume was called the excretion time. When all tests were completed the average excretion time for the ten cages was calculated and this value constituted the bioassay value for that test run. Whenever possible urines for assay were collected on consecutive days and tested with different groups of rats to diminish the effect of biological variations. The same animals were not used more than once a week and after four weeks were discarded and new animals substituted.

### CLINICAL STUDIES, EXPERIMENTAL PROCEDURE

The patients studied were observed in the hospital or ambulatory clinic. Two patients (D. R. and R. B.) had acute hemorrhagic Bright's disease, and two (A. R. and T. H.) had manifestations of acute hemorrhagic Bright's disease with severe renal failure following treatment of pneumonia with

sulfapyridine. These four patients had well developed edema during the acute manifestations of nephritis and had normal plasma proteins throughout. All made a recovery from their disease or complications.

Three patients, two adults (W. H. and A. T.) and one child (S. W.) had the nephrotic syndrome with well marked hypoproteinemia, edema, and varying degrees of renal insufficiency. In each of these patients we observed spontaneous changes in edema unaccompanied by significant changes in the plasma proteins.

In three patients with the nephrotic syndrome the effect of daily administration of pitressin for one week was observed.

One patient had marked recurrent premenstrual edema. At this time her weight gain amounted to from 2 to 8 kilograms. Her plasma proteins were normal and otherwise she appeared to be normal. This patient was also given pitressin for six days and her urine studied during this interval.

Three patients had diabetes insipidus. Their blood chemistry and urea clearance were normal.

Two patients\* had Cushing's syndrome with normal plasma proteins; urea clearance within the lower limit of normal and intermittent edema. Measurements of venous pressures were within normal limits.

In addition, numerous single observations were made on nephrotic patients currently in the hospital, and 11 apparently healthy members of the hospital and laboratory technical staffs were used for normal control observations. Twenty-four hour urine specimens were collected from this group of patients at irregular intervals. No limitations of fluid intake, diet or activity were enforced during periods of urine collection.

## RESULTS

Serial tests on several of our patients could not be run because of toxicity of the urine concentrate. On several occasions urine obtained from a patient which previously had been satisfactory would kill all of the rats injected. We were not able to relate this toxic effect to the patient's disease, clinical condition, or to previous injections of the rats. Undoubtedly a varying amount of this toxic material was usually present in the urine as it was not uncommon to lose one or two of 60 rats. Some of the variations in individual tests may have been due to this factor. The urines used were freshly obtained and it was unlikely that the toxic factor resulted from changes occurring subsequent to voiding.

The average time required for the rats to excrete the arbitrary urine volumes after the animals were injected with material obtained from normal individuals was 142 minutes, the standard deviation was  $\pm 12$  minutes. The normal range was obtained by assuming that 2.66 times the standard

\* We are indebted to Dr. Ephraim Shorr of the New York Hospital for the opportunity to study two of his patients, one with diabetes insipidus and one with Cushing's syndrome.

deviation provided an adequate margin for biological variation. This range and the actual determinations are shown in figure 1.

The two patients (D. R. and R. B.) with acute hemorrhagic Bright's disease, had a significant amount of the antidiuretic material in their urines when they were edematous. After loss of edema the urine from one of the patients (R. B.) had less than the expected normal average diuretic effect (figure 2). The urines from the two patients (A. R. and T. H.) with nephritis following sulfapyridine therapy of pneumonia, showed a marked antidiuretic effect at the time they had edema (figure 2).

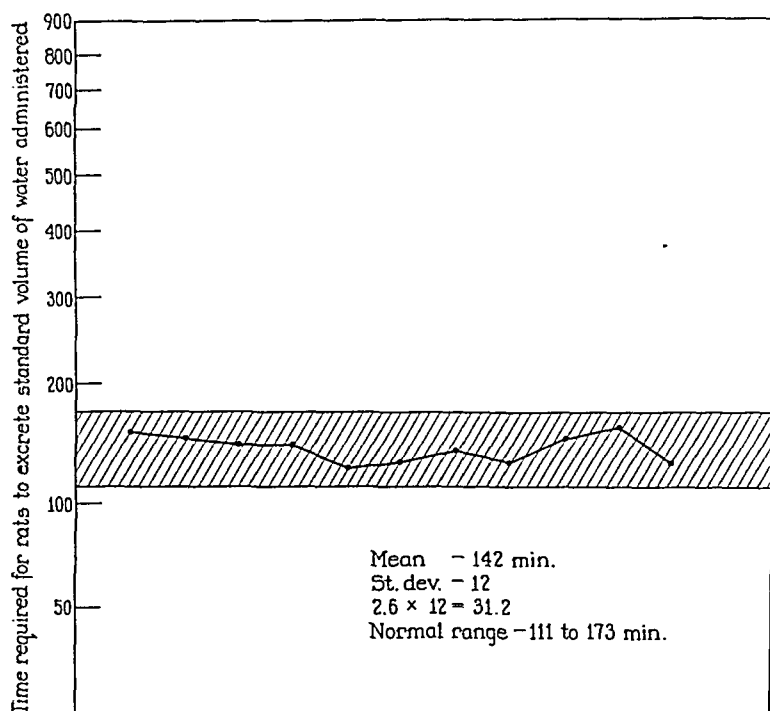


FIG. 1. The antidiuretic titer of urines from 11 normal individuals. The figures on the left represent minutes after administration of the second gavage and intraperitoneal injection of the urine concentrate. The normal range is shown by the shaded area.

The urine from hypoproteinemic, edematous patients with the nephrotic syndrome almost uniformly contained considerable quantities of the anti-diuretic material. Spontaneous changes in edema without plasma protein changes were seen in three of these patients. The comparisons of their tests before and after edema loss are shown in figures 3, 4 and 5. The urine from S. W. tested frequently over a two-month period showed no consistent trend over this interval though her weight was steadily decreasing (figure 3). At the beginning of this two-month interval the patient had pitting edema over the sacrum and lower extremities. During this time the antidiuretic effect of the urine was marked. After about two weeks she began gradually to lose her edema and at the end of the two months was apparently edema-free.



There had been no increase in her plasma proteins. On two occasions during the time of edema loss, the antidiuretic effect of her urine was within the normal range. At the end of the two-month period the patient's plasma albumin had fallen from 1.17 to 1.05 grams per 100 c.c. and the antidiuretic effect of her urine had returned to a maximum. Subsequently she regained her edema in part with no change in the antidiuretic quality of the urine. In this instance there was no clear parallel between the urine assay and the patient's clinical condition. The same variability was found in the urine assays on W. H. during a period of edema (figure 4). However, with the

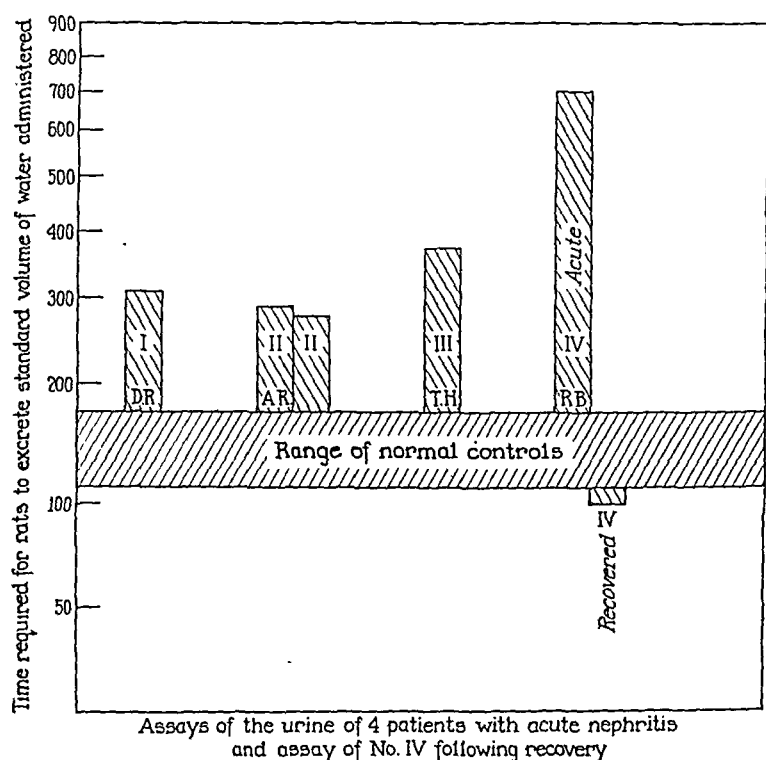


FIG. 2. The assay of 4 patients with edema and nephritis without hypoproteinemia are shown by the height of the vertical columns. Assays on R. B. while edematous and after recovery are shown. D. R. and R. B. had acute hemorrhagic Bright's disease. T. H. and A. R. had manifestations of acute nephritis with edema following sulfapyridine therapy of pneumonia. The time is in minutes.

loss of 17 kilograms of edema the assay of this patient dropped to just outside the normal range and she went for several months edema-free with no change in her plasma proteins. In A. T. the presence of antidiuretic material in the urine correlated closely with the presence of demonstrable edema (figure 5).

The two patients with Cushing's syndrome frequently excreted urine with a marked antidiuretic effect (figures 6 and 7). The initial loss of edema by L. M. was paralleled by a decrease in antidiuretic titer of her urine

but a subsequent increase in the quantity of antidiuretic material in the urine was not accompanied by edema. Amelioration of some of the symptoms of the disease by continuous estrogenic therapy may have complicated the test during a part of the time as subsequently the patient's edema recurred on several occasions when estrogenic therapy was discontinued.

The urine of the patient with menstrual edema showed only a moderate antidiuretic effect during the edematous period but during the intermenstrual non-edematous interval had no antidiuretic effect whatever.

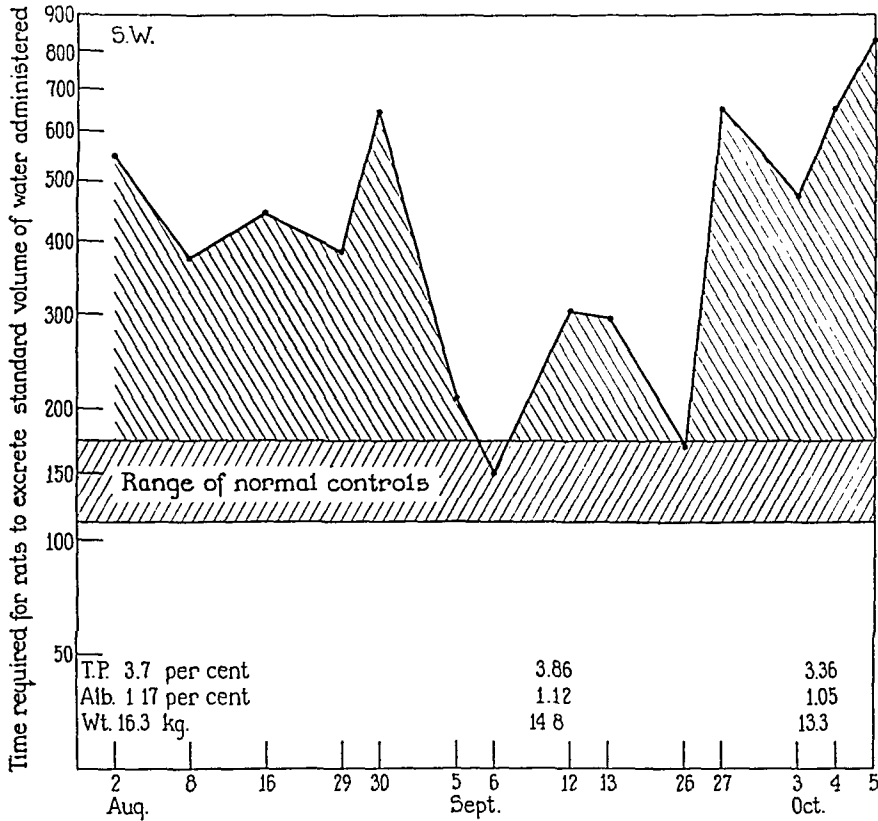


FIG. 3. The assay of S. W., a child with the nephrotic syndrome. This patient lost edema steadily throughout August and September. The plasma proteins also tended to fall. Two assays fell within the normal range but all others were significantly antidiuretic. There was no clinical explanation for lack of correlation between edema loss and antidiuretic titer of the urine. The time is in minutes.

Daily administration for seven days of 30 units of pitressin to four patients was accompanied initially by sharp increases in antidiuretic titer of the urines. This was observed both in patients with antidiuretic and normal urine before pitressin administration. With continued pitressin administration there was a decreased antidiuretic effect from the urine. After four to five days no antidiuretic material in the urine of any of the patients could be demonstrated even though pitressin administrations were continued (figures 8 and 9). The disappearance of antidiuretic material from the urine

paralleled the loss of edema acquired after beginning pitressin administration. No further diuresis occurred in any of our nephrotic patients so treated even though the rat assay fell well below the normal range.

The urine from three patients with diabetes insipidus showed no antidiuretic effect in rats. On the other hand, it did not show any diuretic effect similar to that noted in our patients after pitressin administration.

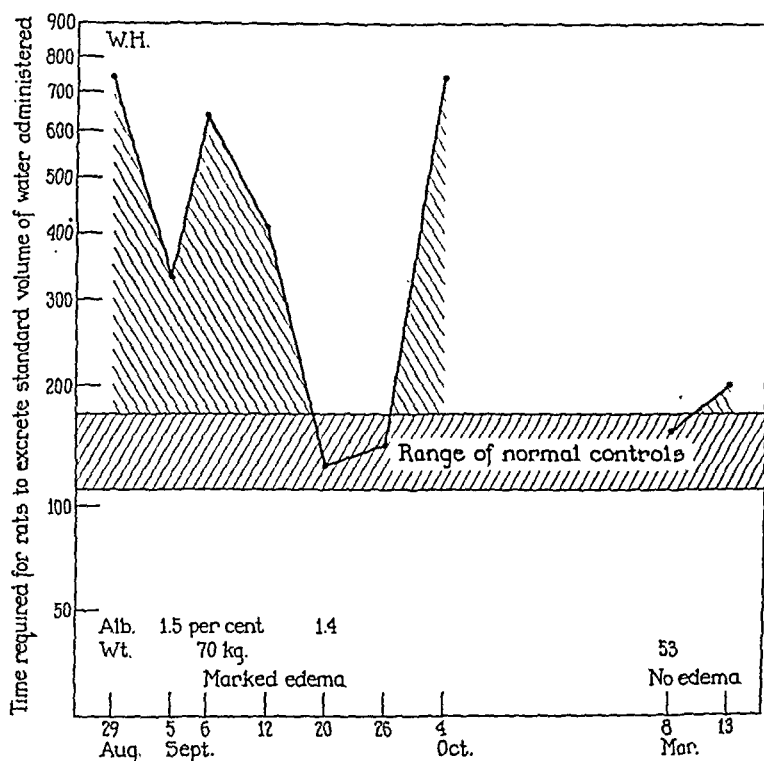


FIG. 4. The assay of W. H. during edematous and non-edematous periods. The two normal values obtained during the period of edema could not be explained on the basis of abrupt clinical changes or laboratory findings. The time is in minutes.

## DISCUSSION

One of the most constant results we obtained was the rapid decrease in antidiuretic effect of the urine while the patient was under continuous pitressin administration. The paradoxical induction of diuresis by pitressin administration was previously noted by McQuarrie, Thompson and Ziegler<sup>9</sup> and suggested as a possible treatment of nephrotic edema. It would appear that the patients either destroy pitressin so administered and in so doing decrease the amount normally available to the body, or that they elaborate a physiological antagonist very rapidly. The marked diuretic effect of urine after six days of pitressin administration would favor the latter hypothesis. We have no explanation for the fact that in our nephrotic patients diuresis was sufficient only to remove water retained under the influence of pitressin and did not affect edema fluid previously present.

Teel and Reid,<sup>10</sup> in a recent study of the urine from women who were normally pregnant and those with preëclampsia and eclampsia, found that in the women with toxemia a large majority produced urine containing considerable antidiuretic activity. Although they were interested in relating the results of the bioassays to the presence of toxemia of pregnancy, they stated that the results paralleled only the presence of edema and could not be corre-

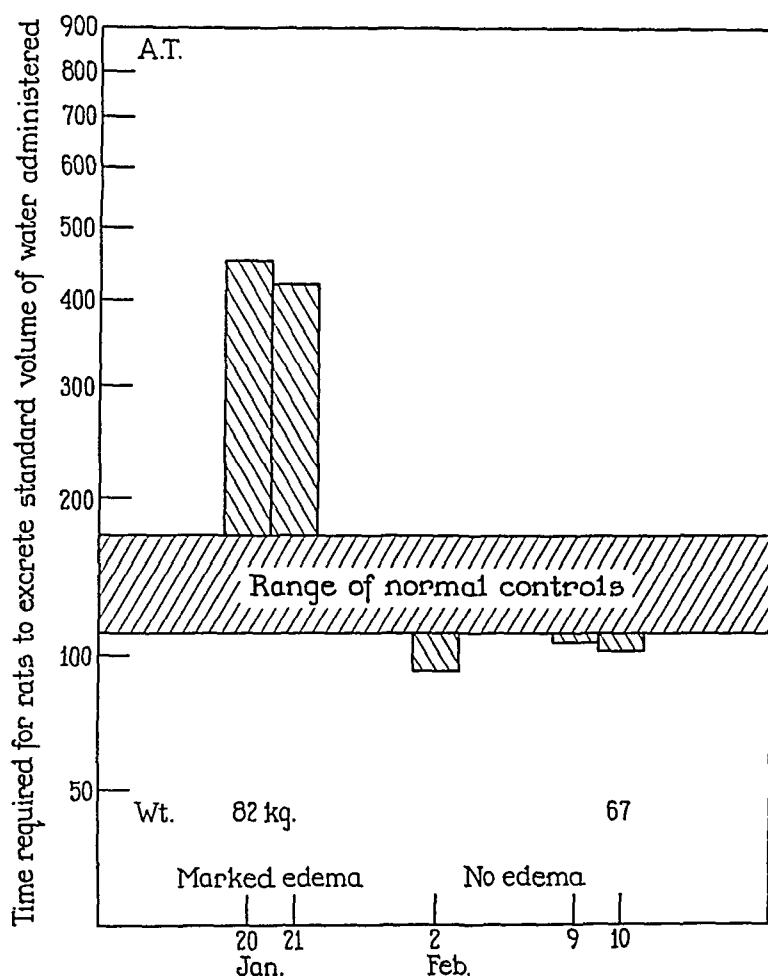


FIG. 5. The antidiuretic values of A. T. correlated with presence or absence of edema. There was no significant change in the patient's plasma proteins during this period of edema loss. The time is in minutes.

lated with albuminuria or hypertension. They found, as have we, that some patients with edema showed no increased antidiuretic titer in the urine, and the urine from an occasional non-edematous patient showed an antidiuretic effect outside of the normal expected range. They carried out studies of the adsorption of the material by urine protein and stated that otherwise potent urine might be rendered inactive due to adsorption of the

principle on protein which in their technic was removed. We found that in our patients the activity persisted without removal of protein. Teel and Reid made no statement of toxic effects from the urine such as we encountered. We were unable to remove the toxic factor by removal of the proteins in one attempt.

Although Teel and Reid <sup>10</sup> in their study in humans, and Ingram, Ladd and Benbow <sup>11</sup> in a study of cats, interpret their results as offering support for the suggestion of Gilman and Goodman that the antidiuretic factor in the urine is derived from the neurohypophysis, Walker <sup>12</sup> has brought forth evi-

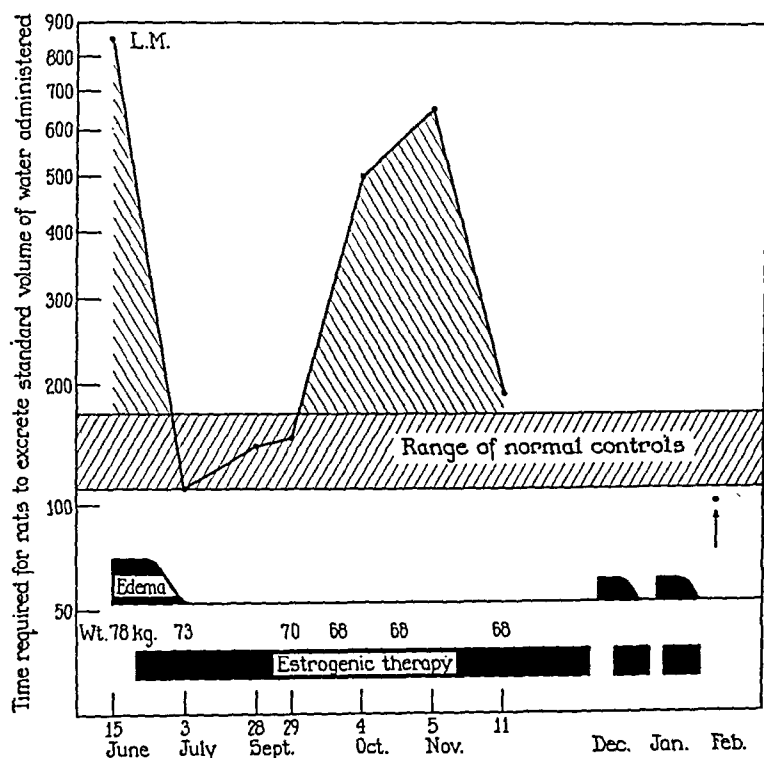


FIG. 6. The initial loss of antidiuretic potency in the urine of L.M. correlated with loss of edema. Intensive estrogenic therapy subsequently instituted may have altered the usual response as on two occasions edema returned when estrogenic therapy was suspended. One assay done in February, when the patient was edema-free and was not receiving estrogenic therapy, showed a value below the expected range. The time is in minutes.

dence that this is not likely. He used not only the rat assay method of Burn but also a very sensitive rabbit assay method which he devised. He failed to find any definite support for the pituitary theory of water diuresis. He was, however, able to confirm the finding of an antidiuretic substance in the urine of dehydrated animals when the method of Gilman and Goodman was used throughout.

Very recently Hare <sup>13</sup> has reported work of significance in regard to the nature of the antidiuretic substance. Hare used dogs with surgically in-

duced diabetes insipidus as his test animals. In these animals the diabetes insipidus could be controlled very satisfactorily by the use of pitressin. Hare used as his test, not simple urine excretion but changes in the creatinine

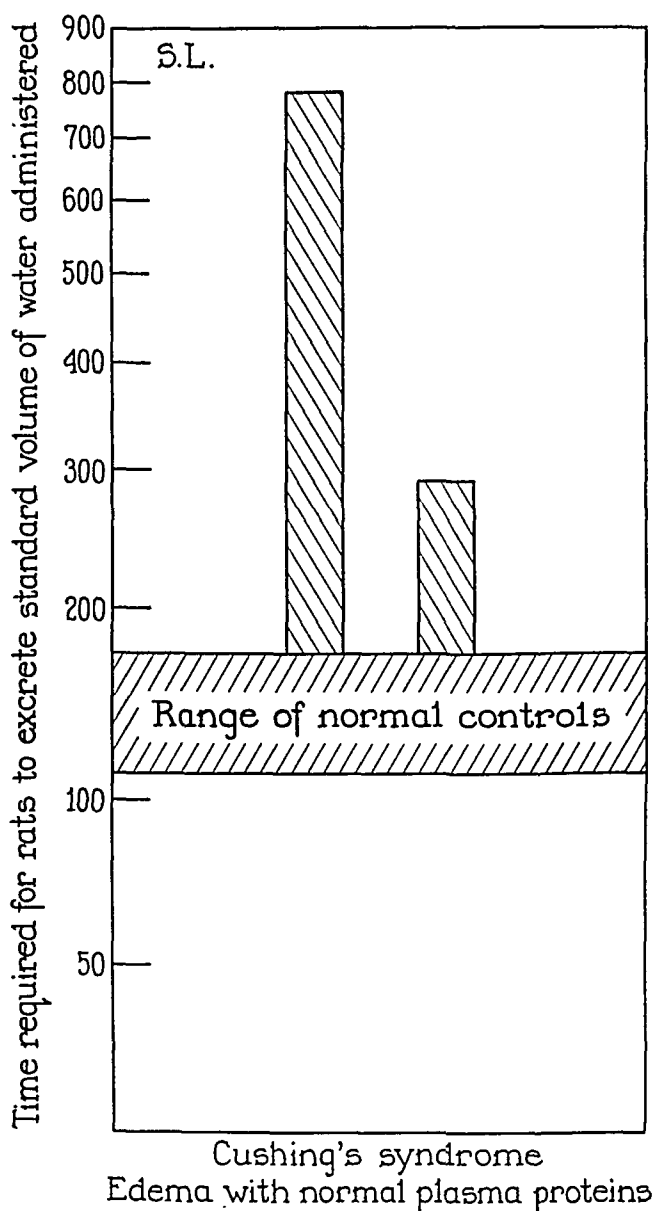


FIG. 7. Two assay series on a patient with Cushing's syndrome while edema was present. Both show marked increase in antidiuretic titer of the urine. The time is in minutes.

clearance. He found that dehydrated normal dogs excreted an antidiuretic substance in the urine and that the urine from these dogs contained a principle which would control the diabetes insipidus in the test animals. Urine

from dehydrated diabetes insipidus dogs had no effect under the same circumstances. Although this work does not give proof of the pituitary origin of the antidiuretic substance, it strongly supports the hypothesis that the pituitary plays an active rôle in the elaboration of the material. We did not carry out any studies on the origin or chemical nature of the material.

In view of the difficulties of interpreting the results obtained under controlled experimental conditions, it is obvious that we can offer no valid suggestions as to the cause of discrepancies which we have observed in some of

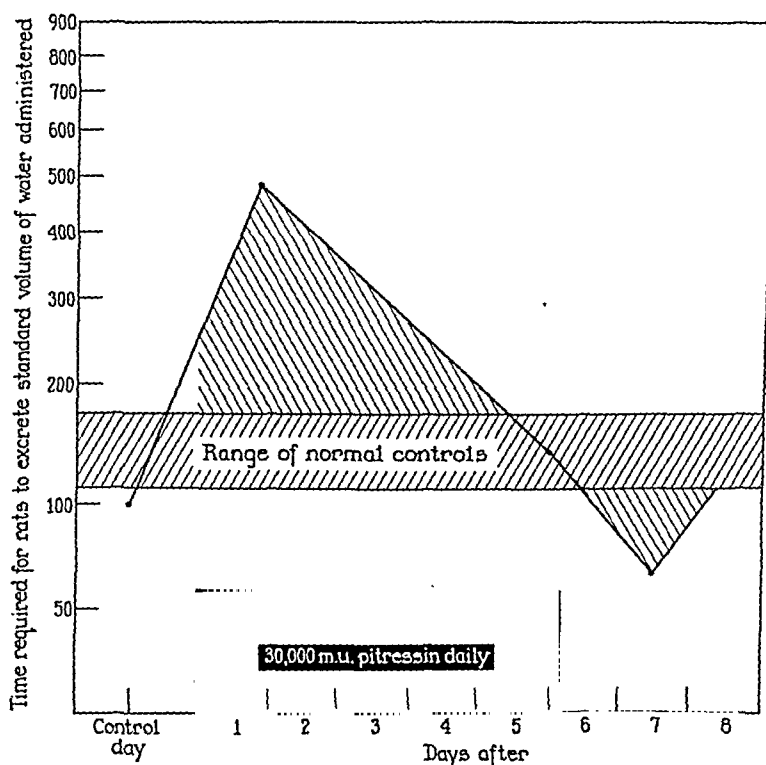


FIG. 8. The effect of continuous pitressin administration on the antidiuretic titer of urine obtained from a slightly edematous nephrotic patient. Note the marked increase in titer initially followed by a progressive fall, with the urine becoming actually diuretic on the fifth and subsequent days of pitressin administration. The time is in minutes.

our serial tests. On the other hand, the reproducibility of the results generally and the correlation with the presence or absence of edema in patients, and the uniform response which we were able to obtain after pitressin administration indicate that the results obtained by this method of assay cannot be artefacts. Doubt concerning the exact nature and derivation of the active principle does not impair its usefulness as a tool for the correlation of certain otherwise unrelated and unexplained facts of edema manifestations in patients.

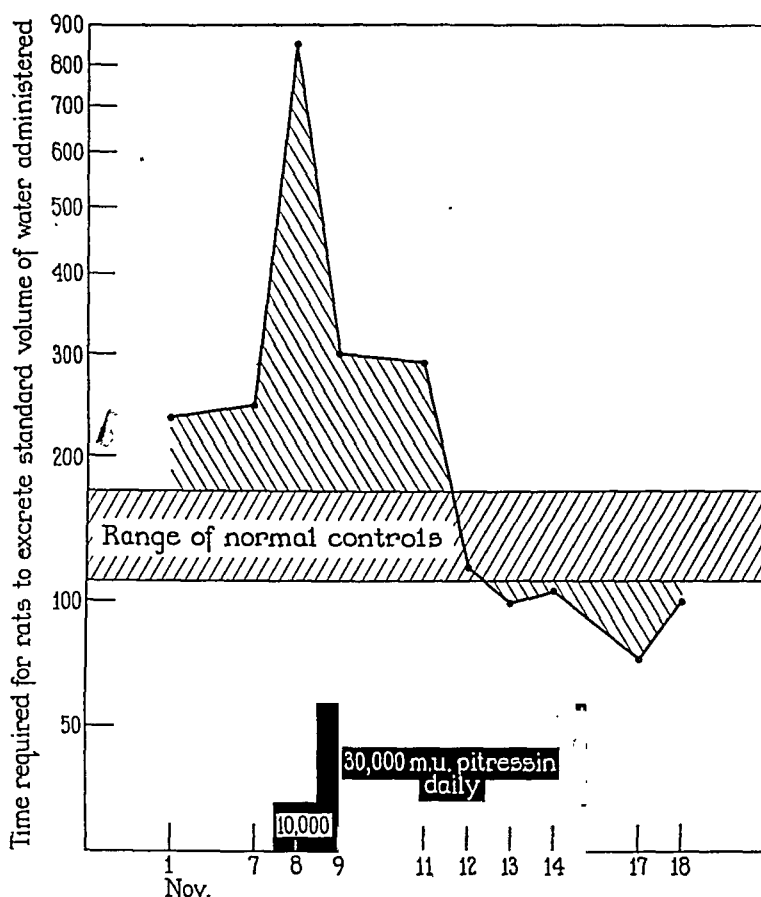


FIG. 9. The effect of continuous pitressin administration in the antidiuretic titer of urine obtained from a non-edematous nephrotic patient. The initial increase was followed by a fall to diuretic levels at the end of the period of pitressin administration. This response was quite uniform and could also be elicited in non-nephrotic subjects. The time is in minutes.

### SUMMARY

Rat bioassays of the urines of patients with Bright's disease, premenstrual edema, Cushing's syndrome and diabetes insipidus, showed a correlation between the presence of clinical edema and the presence of an antidiuretic effect in concentrates of these urines.

This antidiuretic substance, demonstrable in the urines of three edematous patients with the nephrotic syndrome, was no longer demonstrable in the urine of two patients after all had become edema-free. The loss of edema occurred without rise in plasma proteins.

This antidiuretic substance was found in the urine of four patients with manifestations of acute nephritis whose edema could not be explained on a hypoproteinemic basis. In one patient studied after recovery, the antidiuretic substance was no longer present.

Four patients were given 30 units of pitressin parenterally daily for seven days. The antidiuretic effect of urine from these patients reached a maxi-



mum the first day of administration, thereafter decreased rapidly to the normal values. In three patients the urine became diuretic on the sixth day of continuous pitressin administration. The decrease in antidiuretic titer of the urines was paralleled by loss of edema initially resulting from pitressin administration.

Some limitations of the method were discussed.

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# THE TREATMENT OF CHRONIC ULCERATIVE COLITIS WITH SULFANILAMIDE \*

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DURING the past three years, sulfanilamide and its derivatives, such as neoprontosil and more recently sulfapyridine, have been used in the treatment of chronic ulcerative colitis. In this disease several types of organisms are commonly isolated from rectal scrapings and stools. When the same types of organisms are the cause of disease in other parts of the body, the use of the chemotherapeutic agents mentioned has proved valuable in certain instances. Therefore, it seems logical that patients having chronic ulcerative colitis, a serious and disabling disease, should be given the benefit of a trial on this form of therapy.

In this presentation, an attempt will be made to appraise the use of sulfanilamide in the treatment of a series of 33 cases. Neoprontosil alone was the chief chemotherapeutic agent in another group of five cases, and was used subsequent to sulfanilamide therapy in six additional cases. Therefore, a total of 44 cases comprises the basis of this report. Since sulfapyridine has been available only in recent months, an adequate period of time has not lapsed in which to appraise the use of this drug.

The type of colitis under discussion corresponds to the disease described by Bargen<sup>1</sup> and Buie<sup>2</sup> as "thrombo-ulcerative colitis." No cases of regional enteritis, so-called "right-sided" colitis, or the segmental forms are included. This report deals with diffuse, inflammatory, destructive, and hyperplastic processes which are seen by procto-sigmoidoscopic examinations to start in the rectum, and visualized by roentgen examination to extend in an upward direction in the colon.

## MODE OF ADMINISTRATION

When we first started using sulfanilamide three years ago, it was given orally in nontoxic cases and parenterally in severely toxic cases. An attempt was made to maintain a blood sulfanilamide level of between 8 and 10 mg. per 100 c.c. Toxic effects were observed quite commonly. We then tried giving sulfanilamide in smaller doses by retention enema (0.8 per cent solution). In the patients who made a satisfactory response, there were fewer toxic reactions, particularly less nausea, and it was thought that the results obtained by this method of administration were more satisfactory than when the drug was given by mouth. It was also thought that the direct contact of the drug with the mucous membrane might have an additional effect to that obtained by its presence in the systemic circulation.

\* Read at the Cleveland meeting of the American College of Physicians, April 3, 1940.

In most of the cases where sulfanilamide was used, the drug was given by retention enema. A total of 45 grains in 24 hours has not been exceeded. This has resulted in maintaining a blood sulfanilamide level as high as from 5 to 7 mg. per 100 c.c. in certain instances. When possible, treatment is started in the hospital where the patient can be observed closely and daily blood counts can be made. If the drug is well tolerated, it is used for ten days or two weeks, then on alternate weeks in courses of two or three months with an interval of rest of one to three months after each course, depending upon the clinical course and the results of the progress examinations.

At the start of the treatment, one or two opium suppositories may be used daily. The sulfanilamide retention enemas are given four times daily but are not given close to meal time because of the gastrocolic reflex. A 45 grain powder of sulfanilamide is dissolved in a pint of warm distilled water, about one-fourth of this amount (125 c.c.) being again warmed to body temperature just before using as a retention enema. Men who later return to work may use from one-third to one-half of the pint at a time, depending on how many times daily it is convenient to take the enemas. As time goes on, the dosage of the drug or the frequency of its use is often reduced until it is used one week out of every three or four weeks. Because of the tendency of the disease to recur, we have found that it is important to use the drug in intermittent courses for some time, even after there is no evidence of activity.

When neoprontosil became available, we started using this derivative of sulfanilamide in alternate cases for a time, particularly in patients in whom close observation was not possible. The lower toxicity of neoprontosil in the treatment of chronic ulcerative colitis is established and it has been given by mouth only. At the start of treatment, 15 grains are given an hour before each meal, at bed-time, and at 3:00 a.m., a total of 75 grains per 24 hour period. The method is similar to that used by Brown, Herrell, and Borgen.<sup>3</sup> The initial period of use and its intermittent use thereafter are similar to those for sulfanilamide. If progress is favorable, the 3:00 a.m. dose is soon stopped so that 60 grains are received per 24 hour period. With continued improvement, the dosage is reduced further and the periods without the drug are lengthened.

In severely ill hospital patients who respond favorably to the use of either sulfanilamide or neoprontosil, our present impression is that results are obtained more quickly with sulfanilamide retention enemas than with the oral use of neoprontosil. Therefore, in certain instances, we have used sulfanilamide at the start of the treatment and have changed to neoprontosil before the patient is discharged from the hospital, and then continuing with the intermittent use of neoprontosil thereafter. We also have had this experience: The patient may have been started with neoprontosil and either developed an intolerance to the drug or the clinical course may not have been satisfactory, and he was advised to return to the hospital. Changing to sulfanilamide in this instance may result in a favorable course. At the

present time, neoprontosil is being used more frequently than sulfanilamide, particularly in the milder cases, because it is less toxic and oral administration is more convenient.

In recent months, the use of sulfapyridine by mouth in as small a dosage as 0.5 gram ( $7\frac{1}{2}$  grains) four times daily, over a period of 10 days to two weeks at the start of treatment and then on alternate weeks in regular courses as mentioned above, has proved valuable. If a favorable response is noted, there is usually relief of symptoms soon after the drug is started and definite improvement in the proctoscopic findings may be noted within a period of a few weeks.

Soon after the report of McGinty, Lewis, and Holtzclaw <sup>4</sup> was published, stating that the administration of 50 mg. of nicotinic acid three times daily decreased the toxic symptoms experienced by patients receiving large amounts of sulfanilamide, we started using nicotinic acid in our patients at the times they were receiving sulfanilamide. In a few cases, studies were made on the urinary excretion of porphyrin-like substances before and after the administration of nicotinic acid but the results were contradictory. Vitamin deficiency states in the individual cases were probably a factor. However, since the administration of nicotinic acid has seemed to prevent toxic symptoms in certain instances, it is now routinely prescribed in cases of chronic ulcerative colitis when sulfanilamide is being used. Because of the lower toxicity of neoprontosil, nicotinic acid has not seemed to be indicated during the administration of this drug. Methylene blue has not been used in any of the cases in this review.

#### CLASSIFICATION OF CASES

Previous reports <sup>5, 6</sup> have stated the difficulties in classifying cases, in appraising any single therapeutic measure in the treatment of chronic ulcerative colitis, or in comparing the results of one series of cases with another. Each case presents an individual problem. The variable severity of the disease and the fact that it is characterized by spontaneous remissions of symptoms and acute exacerbations must always be kept in mind. Progress proctoscopic examinations may reveal no change in the pathological process even though there has been a complete remission of symptoms. Jones <sup>7</sup> has mentioned that the rectal mucosa would seem to have immunized itself in these instances. Therefore, progress proctoscopic examinations are essential in judging the course of the disease.

In grouping cases, the use of Kiefer's classification of chronic ulcerative colitis <sup>8</sup> has proved helpful (table 1).

TABLE I

##### Kiefer's Classification of Chronic Ulcerative Colitis

- |            |                                    |
|------------|------------------------------------|
| Group I.   | Non-toxic, afebrile, non-sclerotic |
| Group II.  | Non-toxic, afebrile, sclerotic     |
| Group III. | Toxic                              |

Although Kiefer has not observed a close correlation between the clinical severity and the amount of colon involvement, in our experience the cases which have been placed in Group I are usually early cases, and in most instances, the morbid process, as shown by roentgen examination, is limited to the rectum and sigmoid colon. In our present series of cases, we have not seen a case where evidence of toxicity is lacking in Kiefer's Group II. Therefore, in this review, the cases will be placed into either the non-toxic, afebrile group, or the toxic group. The extent of the process as revealed by roentgen examination and other criteria used by Brown, Herrell, and Barger<sup>3</sup> will be quoted.

Table 2 gives a report of the use of sulfanilamide in a nontoxic, afebrile group of cases.

TABLE II  
Afebrile Cases, Sulfanilamide

Case	Duration of Disease in Years	Daily Number of Stools	Roentgen Evidence of Extent of Disease	Last Proctoscopic Examination	Duration of Follow-up in Months	Clinical Results
1	10	4-10	R.S.	Quiescent	35	1
2	6	15+	R.S.	Norm. muc.	30	1
3	4	6-9	R.S.	Quiescent	29	1
4	1	2-4	R.S.		29	3
5	1	15+	R.S.		25	3
6	2	2-4	R.S.	Improved	24	3
7	13	6-8	R.S.		23	1
8	2½	3-6	R.S.	Quiescent	18	1
9	6	4-6	R.S.	Norm. muc.	17	1
10	5	4-16	R.S.	Norm. muc.	16	1
11	3	2-4	R.S.		16	1
12	1	3-6	R.S.	Quiescent	12	2
13	6	15+	S.F.	Quiescent	7	?*

Key: R.S.—rectum and sigmoid  
S.F.—splenic flexure.

1—complete and continuous remission

2—mild recurrence with recovery

3—unsatisfactory response.

\* See case report.

In the tables no mention is made relative to age or sex incidence. Although this disease may occur at any age, it develops mostly in young adults between the ages of 20 and 40 years. The sex incidence is about equal. The heading, "duration of disease in years," includes the time of onset of the disease until the time that sulfanilamide therapy was started. The disease may have existed intermittently during the times stated. The severity of the disease in each individual case cannot be described accurately. However, the duration of the disease, the number of stools passed daily, and the extent of involvement at the time of the initial examination give some idea of the severity and the degree to which the patient was incapacitated by this disease.

In each case, smears and cultures were made from rectal scrapings and from stools as soon as they were passed. There was no evidence of parasitic infection. The initial proctoscopic examination in all cases revealed a diffuse inflammatory process, as defined above, and in every case the disease was active at the time sulfanilamide therapy was started. The findings on progress proctoscopic examinations by us and the duration of follow-up studies are quoted. In the instances where no progress proctoscopic findings are given, these examinations may have been made elsewhere, but not in the Cleveland Clinic. The term "quiescent" means that there was no evidence of activity at the time of the proctoscopic examination. Some scarring of the mucosa or contracture of the lumen may have been present, but no bleeding was observed on swabbing. Since it is possible for a patient with this disease to have a remission for three years, the word "cure" is not mentioned.

#### AFEBRILE, NON-TOXIC CASES

In an analysis of table 2, it will be noted that in eight, or 60 per cent of the 13 cases, the patients have had a complete and continuous remission, in several instances over a period of more than two years. In 10, or 76 per cent, sulfanilamide was considered valuable, and was the only special form of treatment used. Case 13 was a man who was severely incapacitated by this disease at the time sulfanilamide therapy was started, 32 months ago. We previously had used several types of treatment, including autogenous vaccines, without obtaining desirable lasting effects. He made a favorable response to sulfanilamide therapy and returned to work within one month. Several progress proctoscopic examinations over a period of the next seven months revealed a quiescent stage of the disease. He has not been observed since that time.

It will be noted that roentgen examinations in this group of non-toxic cases revealed no evidence of extension of the disease above the sigmoid colon, with the exception of one case where it had extended to the splenic flexure.

#### TOXIC, FEBRILE CASES

Table 3 shows that in 10 cases receiving medical management to date, which are placed in Kiefer's Group III (febrile-toxic), only four or 40 per cent have obtained a complete and continuous remission. In case 10 the referring physician recently stated that the patient's general condition is much improved but there has been incomplete relief of symptoms. This patient originally had had a high fever and had been bed ridden. She is working daily now and is taking sulfanilamide one week in every four weeks.

Table 3 does not include an additional group of five severely toxic cases in which ileostomy or other surgical procedures were used after sulfanilamide therapy failed. In two of these cases, multiple perforations were found at

TABLE III  
Toxic, Febrile Cases, Sulfanilamide

Case	Duration of Disease in Years	Daily Number of Stools	Roentgen Evidence of Extent of Disease	Last Proctoscopic Examination	Duration of Follow-up in Months	Clinical Results
1	5	10-15	E.C.		37	3
2	$\frac{2}{3}$	15+	H.F.	Quiescent	30	1
3	14	15+	H.F.	Improved	30	1
4	10	9-10	S.F.	Quiescent	28	3
5	3	3-10	S.F.	No change	26	3
6	$1\frac{1}{2}$	15+	E.C.	Quiescent (polyps)	24	3
7	3	3-4	R.S.	Normal (contrac.)	23	1
8	11	15+	R.S.	Imp. then recur.	20	3
9	3	9	E.C.		14	1
10	$\frac{2}{3}$	12-15	R.S.		9	?

Key: R.S.—rectum and sigmoid  
S.F.—splenic flexure  
H.F.—hepatic flexure  
E.C.—entire colon.

1—complete and continuous remission  
3—unsatisfactory response.

the time of operation and it was believed that this situation existed prior to the institution of sulfanilamide therapy. Death occurred in both instances.

Death occurred in two other severely toxic cases in which sulfanilamide therapy had been used. One patient who was 76 years of age died after operation for prostatic obstruction. In the other case, sulfanilamide was used for only six days.

Sulfanilamide therapy might have been expected to have a beneficial result in three of the cases in which surgery proved necessary as a life-saving procedure. In combining these three cases with the ten toxic cases receiving medical management, it is apparent that only 30 per cent of this group have had a remission which may be attributable to the use of sulfanilamide.

In tables 4 and 5 is a group of patients in which sulfanilamide and neoprontosil, or neoprontosil alone were given, each at different times. Because of the relatively small series of cases in this group, the non-toxic and toxic cases are grouped together.

In an analysis of tables 4 and 5, eleven non-toxic and toxic cases received sulfanilamide and neoprontosil, each at different times, or neoprontosil alone. Three cases have had a continuous remission, with proctoscopic examinations revealing normal findings; six cases have had mild recurrences with recovery, and in only two cases has this form of therapy been discarded to date. The features which need emphasis in this group are the small number of cases and the relatively short period of follow-up studies. However, consideration is given this group because it shows trends and possibilities in the treatment of this serious disease.

Clinicians who are particularly interested in treating this disease know that any therapeutic procedure which has shown promise of relieving the

patient's disability should be given an adequate trial. In several cases observed in recent months, the use of relatively small oral doses of sulfapyridine has resulted in a favorable response but an adequate period of time has not lapsed in which to appraise the use of this drug.

TABLE IV  
Sulfanilamide and Neoprontosil (Oral)

Case	Group	Duration of Disease in Years	Daily Number of Stools	Roentgen Evidence of Extent of Disease	Last Proctoscopic Examination	Duration of Follow-up in Months	Clinical Results
1	S.T.	2½	10-14	E.C.		35	2
2	S.T.	½	6	E.C.	Quiescent	26	2
3	S.T.	¼	Invol.	E.C.	Quiescent	15	2
4	A.	3	12	R.S.	Norm. muc.	10	1
5	M.T.	¼	6-12	R.S.	Recur.	7	3
6	S.T.	1	15+	E.C.	Improved	7	2

Key: A.—afebrile  
S.T.—severely toxic  
M.T.—mildly toxic

R.S.—rectum and sigmoid  
E.C.—entire colon.

1—complete and continuous remission  
2—mild recurrence with recovery  
3—unsatisfactory response.

TABLE V  
Neoprontosil (Oral)

Case	Group	Duration of Disease in Years	Daily Number of Stools	Roentgen Evidence of Extent of Disease	Last Proctoscopic Examination	Duration of Follow-up in Months	Clinical Results
1	A.	27	15+	E.C.	Quiescent (polyp)	11	2
2	A.	2	3-4	R.S.	Norm. recur.	11	2
3	M.T.	7	15+	S.F.	Norm. muc.	7	1
4	M.T.	1	7	S.F.	Norm. muc.	7	1
5	M.T.	3	8-10	E.C.	Improved	8	3

Key: A.—afebrile  
M.T.—mildly toxic  
S.T.—severely toxic

R.S.—rectum and sigmoid  
S.F.—splenic flexure  
E.C.—entire colon.

1—complete and continuous remission  
2—mild recurrence with recovery  
3—unsatisfactory response.

### OTHER FORMS OF TREATMENT

It is difficult to evaluate any single therapeutic measure in this disease because the plan of management has included well-known factors pertaining to diet, rest, vitamin and mineral deficiencies, and the administration of blood transfusions and parenteral fluids in severely toxic cases.<sup>9</sup> Mackie,<sup>9</sup> Willard, Pessel, Hundley and Bockus<sup>10</sup> and many others have emphasized the need for a multiple approach in the treatment of chronic ulcerative colitis. There-



fore, sulfanilamide and/or its derivatives should be considered as an *adjunct* to the usual therapy and certainly not as a specific remedy. However, in many of the cases cited in this review, this adjunct was not used until after the usual forms of therapy had proved ineffective. No patient who has made a favorable response to sulfanilamide therapy has received sera or vaccine since this form of chemotherapy was instituted. In our experience, when a patient makes a favorable response to this form of therapy, this occurs more quickly than has been observed with other forms of medical management. A decision relative to its effectiveness is usually made within seven to fourteen days.

The effective treatment of chronic ulcerative colitis depends upon the various features presented by the individual case, such as evidence of toxicity, the degrees of deformity or complications in the colon, the duration of the disease, the types of treatment that have already proved ineffective, and the variable severity of the disease in general. The patient may present evidence of irreparable damage at the time of the initial examination. Education of the patient and his family as to the seriousness of the disease, and the usual life history of an individual having this disease is of great importance, at the start of treatment. Certain complications constitute definite indications for surgery, such as stricture, polyposis, neoplasm, and perirectal abscess. In pointing out other indications for surgery, Jones<sup>7</sup> has found that with each acute exacerbation of the disease it tends to extend to more proximal segments of the colon. In all toxic cases, at least, we believe the surgeon should be in constant attendance with the internist. It is hoped that the surgical indications will become as well defined in this disease in the near future as they are now established in the case of peptic ulcer.

The aim of medical management should be not only to produce a remission of the disease but also to prevent the ultimate need for ileostomy, if not colectomy. The decreasing use of surgical procedures in a large series of cases reported by Barga<sup>1</sup> and Buie<sup>2</sup> is significant. However, if medical management does not prevent acute exacerbations, and progress roentgen examinations show that the disease is extending orad in the colon, how long should we wait before instituting surgical procedures? A colostomy (division of the bowel and its mesentery) in the mid-transverse colon results in less disability to the patient than ileostomy. When a patient's progress is not satisfactory on medical management, should this procedure be used earlier in the course of the disease than is customary? If this were done in these instances, possibly the continued use of the newer developments in medical management (as they appear) would permit the gastrointestinal lumen to be reestablished later.

#### COMMENT

Brown, Herrell, and Barga<sup>3</sup> presented their appraisal of the use of neoprontosil in the treatment of chronic ulcerative colitis before this college one year ago. Our experiences in a smaller series of cases coincide with their

observations. Since sulfanilamide was introduced prior to neoprontosil and the duration of a remission is significant in this disease, our experiences with these forms of chemotherapy were considered worthy of record.

Chronic ulcerative colitis is now recognized earlier in the course of the disease, probably because of the more frequent use of stool, proctoscopic, and roentgen examinations of the colon in any patient who has dysfunction of the colon. We believe our present study indicates that the use of sulfanilamide and/or its derivatives is of greatest significance when used early in the course of the disease.

After an experience of three years, we now routinely give each patient the benefit of a trial on this form of therapy. If the drug is well tolerated, its continuance or discontinuance is based on the response of the individual patient within a period of seven to fourteen days.

### SUMMARY AND CONCLUSIONS

An appraisal is made of the use of sulfanilamide and/or neoprontosil in the treatment of chronic ulcerative colitis during the past three years.

Careful observation of the patient and repeated blood counts must be made during the administration of these chemotherapeutic agents. Three of the patients in this series made a satisfactory initial response to sulfanilamide therapy but later developed an intolerance to the drug. The immediate discontinuance of sulfanilamide resulted in the clearance of these reactions and no patient in this study has had serious sequelae because of this form of chemotherapy.

Death occurred in four instances subsequent to the use of sulfanilamide therapy. All four patients had extensive, if not irreparable damage to the entire colon and were severely toxic at the time of admittance to the clinic. Multiple perforations of the colon were found at the time of operation in two patients, the third patient was 76 years of age and died after an operation for prostatic obstruction, and sulfanilamide was used only six days in the fourth patient.

Ileostomy has been performed on three other severely toxic patients after the failure of sulfanilamide therapy. In combining these three cases with 10 *toxic* cases receiving medical management, a remission which may be attributable to the use of sulfanilamide occurred in only four of this group, or 30 per cent.

In a group of 13 *non-toxic* cases, a complete and continuous remission has occurred in eight or 60 per cent, in several instances over a period of more than two years. In ten or 76 per cent, sulfanilamide was considered valuable and was the only special form of treatment used.

In a general appraisal of the use of sulfanilamide in 26 cases, combining both *non-toxic* and *toxic* cases, in which the use of this drug might have been expected to prove significant, favorable responses were obtained in 15 cases, or 57 per cent.

We therefore believe that sulfanilamide has a place in the treatment of chronic ulcerative colitis. It should be considered an *adjunct* to the usual forms of treatment and not as a specific remedy. It has proved of greatest value in the early non-toxic stage of the disease.

Experiences with neoprontosil and sulfapyridine are mentioned but the small number of cases and the relatively short period of observation since treatment was started permit only initial impressions.

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# CONCERNING THE CORRELATION OF THE PATHOLOGY AND SYMPTOMS OF CORONARY ARTERY DISEASE \*

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THE fact that it is often difficult or perhaps impossible to correlate the pathology and symptoms of coronary artery disease has led to a great deal of discussion and numerous explanations have been proposed. Developments during recent years, however, have contributed much to better understanding of the problem.

Certain aspects of the pathology have a particular bearing on the diverse symptoms. In the first place, it is generally known that the heart may be normal in size in the presence of extensive sclerosis of the coronary arteries. Thus, in 113 cases analyzed by Nathanson,<sup>1</sup> selected because they presented advanced stage of the disease with marked narrowing or obstruction of one or more of the larger arteries, 45 (40 per cent) weighed 400 grams or less. Furthermore, in 12 of the 24 with occlusion of one of the main branches the weight of the heart did not exceed 400 grams. In a series of cases reported by Applebaum and Nicholson<sup>2</sup> the weight of the heart in 25 of the 94 was within the range of normal set at 400 grams. Palmer<sup>3</sup> studied the size of the heart roentgenologically in 200 patients who had survived coronary thrombosis by at least three months. About one-third of the series failed to show or to develop definite cardiac enlargement although observed over a period averaging more than three years following the coronary accident and despite the fact that several had subsequent attacks.

Jores<sup>4</sup> and others have pointed out that the arteriosclerotic process involves mainly the larger and medium sized vessels and that the arterioles are rarely concerned. Saphir, Priest, Hamburger, and Katz<sup>5</sup> from the study of 34 hearts with advanced disease of the coronary arteries found no relation between the gross lesions in the larger branches and the histological changes in the smaller vessels (arterioles). They stated that often the latter showed no significant alterations in the presence of pronounced arteriosclerosis of the larger arteries; that intimal thickening of the arterioles was disclosed in only a few sections from the myocardium and that obliterating endarteritis was not observed in a single instance. Moreover, in the arteriolar sclerosis of hypertension the arterioles are usually implicated to a minor extent as compared to the degree of involvement found in other organs.<sup>6</sup> This is of great significance, for the smaller branches serve an important function in the development of collateral circulation.

\* Read at the Cleveland meeting of the American College of Physicians, April 3, 1940.  
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Disease of the coronary arteries frequently progresses to an advanced stage before symptoms appear. While the condition is generally more extensive in one vessel, particularly the anterior descending branch of the left coronary artery, the other main branches are usually involved to varying extent. This feature was especially emphasized in the report by Saphir and his co-workers. Both coronary arteries were involved in each of the 34 hearts examined. In those with myocardial infarct at least two branches supplying this particular area were involved. The infarction was usually located in the area supplied by the occluded artery. There were instances, however, in which a recent thrombus was found in one vessel and the resulting infarct was located in an area supplied by a previously occluded adjacent artery. These observers also noted the presence of infarct in four instances in absence of occlusion. It was observed, however, that the lumen of these vessels was greatly reduced. Similar results have been recorded by Schlesinger<sup>7</sup> and still more recently by Blumgart, Schlesinger, and Davis.<sup>8</sup> Schlesinger cited one instance in which there was an adequate injection throughout the heart even though both main branches of the left coronary artery and the main stem and the larger branch of the right coronary were occluded. The more recent obstruction concerned the circumflex branch of the left coronary artery but an infarct did not result. Moreover, despite the multiple occlusions of the main branches of the coronary arteries there was very little fibrosis of the myocardium. In this connection it is well to bear in mind that the orifices of the coronary arteries may be obstructed by syphilitic process without the production of infarction, such as in the two cases reported by Leary and Wearn.<sup>9</sup> The hearts weighed 328 and 285 grams respectively and there were no significant histological changes.

There is also great diversity in the extent of the fibrosis of the myocardium, even in the presence of extensive disease of the coronary arteries. Oberhelman and Le Count<sup>10</sup> indicate that there may be no gross or microscopic changes in the cardiac muscle following the closure of either the right or left coronary artery and cite the observations of Galli and Merkel. In the series of 113 cases studied by Nathanson the fibrosis varied from slight to extensive degree. Schlesinger and others have also commented on the variability of this aspect of the pathology.

It is apparent that the heart may withstand repeated major insults to the coronary circulation without gross and perhaps microscopic changes in the myocardium. This can be explained only on the basis of the development of collateral or accessory circulation. The experimental ligation of one of the main branches of the coronary arteries, in my experience, has always produced an area of infarction.<sup>11</sup> It is quite probable that under similar circumstances the same would obtain in man. With normal coronary arteries, therefore, it would seem that if the blood supply to a large area of the myocardium is suddenly interrupted it is not possible for this to be completely restored by an adjacent vessel. The fact that there is rather striking

variation in the size of the resulting lesion when the same vessel is ligated at corresponding levels would indicate at least that in certain instances there is considerable collateral circulation. Anastomosis between adjacent normal vessels no doubt varies in extent, probably effective for the most part through the smaller branches, or perhaps may exist only in a potential state until there is need for it. Wiggers<sup>12</sup> concluded that the communication between normal vessels is extremely small but further states that this does not preclude the enlargement of minute potential channels nor the development of new ones when a main branch is slowly occluded. The investigation by Blum, Schauer, and Calef,<sup>13</sup> however, demonstrated that effective collateral circulation may develop in a relatively short time. These observers studied the effects of gradual occlusion of the anterior descending branch of the left coronary artery in 14 dogs over periods averaging five weeks in duration. In ten of these animals there was no gross evidence of an infarct, and moreover in four there were no histological changes in the myocardium.

It is well known that there is commonly free communication between vessels in which one has been gradually occluded. The need for this is obvious and has been repeatedly emphasized. This question has more recently been investigated by Schlesinger using an improved method consisting of a combination of multicolored radiopaque injection material and complete dissection. In a group of 35 hearts taken from patients over 55 years of age extensive collateral circulation was disclosed in only those instances in which there was occlusion of the coronary arteries. It is of interest to note, however, that anastomosis was demonstrated in five hearts in which the coronary arteries presented only few scattered atheromatous plaques. Wearn and his associates<sup>14</sup> and others have shown that under adverse circumstances the thebesian veins may contribute to the blood supply of the myocardium. Finally, Beck and Tichy<sup>15</sup> and Robertson<sup>16</sup> have demonstrated the importance of extra cardiac circulation. In the investigation by Robertson the coronary sinus, the main veins, and the coronary arteries were successively ligated, and finally in certain instances the pericardial adhesions were later separated. In the typical protocol cited, the first procedure was carried out February 20 and the final one, the sixth, August 18. In the last operation the pericardium was stripped from the myocardium. The dog died in October from cardiac failure. These operations resulted in the development of extensive communications between the vessels of the heart and those of adjacent structures which were regarded as being mainly responsible for the maintenance of the cardiac circulation.

The initial symptom in coronary artery disease is usually either shortness of breath on exertion, sudden onset of dyspnea, angina of effort, or severe anginal pain from coronary thrombosis. In the cases in which the onset is that of the gradual development of shortness of breath the disease of the coronary arteries is often supplemented by other factors such as hypertension, chronic valvular heart disease, etc., which increase the demands on the

heart. The sudden onset of intense dyspnea (acute left ventricular failure) as the first intimation of cardiac disability is usually due to coronary thrombosis. The occurrence of coronary thrombosis without pain is far more common than generally appreciated. In 53 autopsied cases analyzed by Davis<sup>17</sup> there were 21 that did not give history of pain. Others have estimated that 30 to 50 per cent do not have significant distress.<sup>18, 19</sup>

The greatest discussion has been concerned with the explanation of the pain of angina pectoris. Of the numerous theories that have been proposed the concept that the pain results from inadequate blood supply to the myocardium has had the largest following. The identification of the syndrome of coronary thrombosis and the fact that the pain in this condition is indistinguishable from that of angina pectoris except perhaps from the standpoint of intensity again focused attention on the coronary arteries. Subsequent investigations have fully convinced most of those interested in the field that a deficiency in the blood supply to cardiac muscle is the basic factor in the production of the pain in the vast majority of the cases. There are two features in particular, however, that are difficult to explain on this hypothesis. In the first place there are occasional instances such as reported by Leary in which there are no significant changes in the coronary arteries. Furthermore, as emphasized by Saphir and his co-workers it is not possible to determine at necropsy which patients have had pain. Thus, in 18 of their 34 cases there was history of angina pectoris and in a number of these the heart presented coronary thrombosis, arteriosclerotic occlusion, and myocardial infarction. There were others, however, with the same pathological changes that apparently did not experience pain. Furthermore, equally extensive lesions were disclosed in cases in which there was no history of cardiac disability. Blumgart, Schlesinger, and Davis<sup>8</sup> have recently reported an extensive investigation concerned primarily with the relation of the pathologic process to the clinical manifestations of coronary artery disease. Of the 30 cases studied there were 12 in which angina pectoris was the primary condition. Ten of these had old complete occlusion of at least two main coronary arteries. In the remaining two one of the main coronary arteries was closed and the other two were partially obstructed. There were also five cases in which the angina was a later development. In one it was preceded by congestive failure and the subsequent occurrence of coronary thrombosis. Three had advanced rheumatic valvular disease and one cor pulmonale. In one of the cases with valvular heart, that of a young man 26 years of age, there was no demonstrable disease of the coronary arteries. There was a history of repeated recurrence of severe rheumatic infection and the predominating lesion was that of high grade aortic insufficiency, the blood pressure being 200 systolic and 20 diastolic. It was concluded that the anatomical alterations in every case were consistent with the theory that angina pectoris is the result of the paroxysmal occurrence of relative myocardial ischemia. However, the presence or absence of pathological changes

in the coronary arteries was not always the sole factor which determined the presence or absence of angina pectoris.

Angina pectoris in the absence of significant coronary artery disease is undoubtedly rare and is generally associated with factors which impose excessive demands on the heart. Cases of this type have directed attention to other possibilities and of these increased vasomotor tone or spasm has received increasing support from investigations of recent years. The association of indigestion with angina pectoris suggesting reflex connection between the stomach, gall bladder, esophagus, and the heart is a common observation. Von Bergmann<sup>20</sup> reports that the inflation of a balloon in the stomach of the dog produces vasoconstriction of the coronary arteries which is abolished by atropin or section of the vagus. These results have since been confirmed by Gilbert, Fenn, and Le Roy.<sup>21</sup> Morrison and Swalm<sup>22</sup> tried out the effects of distending a balloon introduced into the esophagus or stomach of two patients with angina pectoris. In both the pain was induced and in one there was a pronounced reduction in the cardiac rate. The distress promptly disappeared following the release of the pressure within the balloon. That vasomotor changes may play a rôle in the production of pain is further indicated by the investigation of Hall, Ettinger, Banting, and Manning<sup>23</sup> in which it was shown that it was possible to produce changes in the myocardium by prolonged or repeated vagal stimulation.

There are still wide gaps in our knowledge regarding the explanation of anginal pain. Of the various possibilities, however, it is obvious that the production of pain is dependent on the presence of receptive sensory nerve endings. Katz, Mayne, and Weinstein<sup>24</sup> have demonstrated in the dog that if the nerves accompanying a coronary artery are blocked the obstruction of the vessel apparently does not cause pain. Furthermore, stimulation of the nerves seems to produce the same reaction as the ligation of the vessel and the surrounding structures. Thus, the receptive state of the sensory nerve endings may account for absence or presence of pain. Finally, it is generally known that there is great variation in the individual response to pain. This has been emphasized by Libman<sup>25</sup> and referred to in different connections by numerous observers. Stewart Roberts<sup>26</sup> has stressed this factor in angina pectoris and believes that it is largely responsible for the low incidence of the disorder in negroes.

### CONCLUSIONS

In coronary artery disease the changes in the arteries are the only constant feature. The response of the heart in any particular instance is no doubt influenced by many factors but the ability to maintain an adequate circulation to the myocardium through the development of collateral circulation is perhaps the most important. Clinical and experimental studies have demonstrated that this is more effectively accomplished if there is a gradual occlusion of the vessels. In the normal subject the communications between



adjacent vessels are limited and in most instances by means of the smaller vessels. Therefore, the abrupt closure of one of the main vessels early in the course of the disease usually results in a large area of infarction. If, on the other hand, the obstructive process develops slowly and is not terminated too soon by a thrombus there may be very little or perhaps no significant degeneration of the myocardium. Thus, the rate of the formation of the obstruction determines in a large measure the extent of the collateral circulation, the histological changes in the myocardium, the efficiency of the heart, and quite probably the character of the clinical expression.

Of the various symptoms pain is the most difficult to explain. Most workers in this field believe that insufficiency in the coronary circulation is the basic factor. Two features in particular, however, are difficult to explain on this hypothesis. In the first place, there is an occasional case in which there is no demonstrable disease of the coronary arteries or if present is regarded as being insignificant. Moreover, many with advanced disease of the coronary arteries never have angina pectoris. In the former the angina is usually associated with conditions which impose excessive demands on the heart. There is also the possibility that increased vasomotor tone or spasm may be a factor. Finally, in the cases of extensive disease of the coronary arteries the receptive state of the sensory nerve endings, or perhaps the nervous mechanism in general, may determine the presence or absence of pain.

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# MALARIAL COMA \*

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COMA as the presenting manifestation of disease is a challenge to the diagnostic and therapeutic skill of the physician. This is true not only because coma is often of serious omen but also because an informant is frequently not present and little or nothing can be learned of the history of the illness. The physician must depend in many instances, therefore, on objective findings alone.

The records of all patients admitted in coma to the John Gaston Hospital during the past five years have been reviewed. Of 73,782 admissions, 1,021 were comatose, an incidence of 1.4 per cent.

Many of the articles dealing with coma have failed to mention malaria. One reason for this is that most of the contributions to the subject have come from writers in non-malarial districts. Those of us who practice in localities where malaria is common can attest that it is an important factor in the production of coma. In our series it stood seventh, accounting for 4.7 per cent of all comatose admissions.

TABLE I  
Analysis of 1021 Cases Admitted in Coma

Diagnosis	Number	Per Cent	Diagnosis	Number	Per Cent
Cerebral vascular accident	219	21.4	Cerebral tumor	4	0.4
Head injury	187	18.3	Cerebral arteriosclerosis	4	0.4
Meningitis	114	11.2	Convulsions, unclassified	3	0.3
Uremia	80	7.8	Spasmophilia	3	0.3
Chemical poisoning	59	5.7	Cirrhosis of liver	2	0.2
Lobar pneumonia	56	5.5	Hemorrhage	2	0.2
Malaria	48	4.7	Acute yellow atrophy	2	0.2
Alcoholism	43	4.2	Cerebral abscess	1	0.1
Syphilis of C. N. S.	43	4.2	Pernicious anemia	1	0.1
Toxemia of pregnancy	39	3.8	Electrical shock	1	0.1
Diabetes mellitus	32	3.1	Exposure to cold	1	0.1
Hypertensive encephalopathy	31	3.0	Stokes Adams syndrome	1	0.1
Epilepsy	13	1.2	Acidosis (non-diabetic)	1	0.1
Encephalitis	12	1.2	Hyperinsulinism	1	0.1
Typhoid fever	6	0.6	Diphtheria	1	0.1
Exposure to heat	6	0.6	Ascaris lumbricoides	1	0.1
Hysteria	6	0.6	infestation		

Reference to table 1 will show that in our series the diseases responsible for coma on admission more frequently than malaria were cerebral vascular accident, head injuries, meningitis, uremia, chemical poisoning and lobar

\* Read at the Cleveland meeting of the American College of Physicians April 3, 1940.  
From the Departments of Medicine, University of Tennessee College of Medicine, and John Gaston Hospital.

pneumonia. Alcoholism was a less frequent cause of coma than malaria. It ranked eighth in our series, being responsible for 43 cases, or 4.2 per cent. This is a rather sharp contrast to Solomon's<sup>1</sup> observation in his analysis of the causes of coma on admission to the Boston City Hospital. In his series, 59 per cent were due to alcoholism. This, however, should not be taken to indicate that Memphis is a more temperate city than Boston. In Memphis a special provision is made for the care of the victims of alcoholic intoxication and they are usually not admitted to the John Gaston Hospital.

It is usually easy to explain the fluctuation in the prevalence of malaria, as it is related to the amount of rainfall and other factors influencing the propagation of mosquitoes. The incidence of malarial coma, as well as that of malaria itself, varies considerably from year to year as is shown in table 2. We are not able to explain the fact that in 1935 coma was present in 8.5 per cent of all malarial patients, while in 1939 the incidence was only 0.9 per cent.

TABLE II  
Incidence of Malarial Coma

Year	Total	Coma	Per Cent
1935	327	27	8.5
1936	142	6	4.2
1937	165	7	4.2
1938	164	6	3.6
1939	220	2	0.9

It will be seen from the accompanying graph, figure 1, that there is a very decided seasonal incidence of malarial coma. Most of our cases were admitted in August and October. It will be observed further that not a single case occurred during the months from February to June. This high incidence of coma during the fall is accounted for by the prevalence of estivo-autumnal malaria during that season.

While it is well known that estivo-autumnal malaria generally occurs in the fall and tertian infections are more common in the spring and early summer, the reason for this variation has not been definitely shown. The hypothesis that tertian merozoites prefer reticulocytes to older red blood cells and that reticulocytes are more numerous in the blood in the spring may explain the frequency of that type of infection during that season. No reason is apparent, however, for the seasonal predilection of estivo-autumnal malaria.

A rather unusual feature of our series is that three of our 48 cases were tertian infections. Two other patients were infected with both estivo-autumnal and tertian parasites. The following is a brief résumé of the three tertian cases:

*Case 1.* A negro male, about 40 years of age, was admitted in coma. No informant was present and a history was not obtainable. The admission temperature was 95 degrees Fahrenheit and the patient was in shock. Tertian parasites were present in the blood smear. The patient did not respond to treatment and died 17

hours after admission. He did not regain consciousness. A necropsy could not be obtained.

*Case 2.* A white man, 71 years old, was comatose on admission. The initial temperature was 99.8 degrees Fahrenheit. Tertian parasites were found in the blood smear and in a thick drop preparation. Consciousness returned about 24 hours after admission, the temperature became normal two days later and he was discharged improved at the end of five days.

*Case 3.* A white male, 32 years of age, was admitted in coma. He had been ill for eight days, but the duration of coma was not known. His temperature was 105 degrees Fahrenheit. Tertian parasites were found in the blood smear. Coma continued for two days, the temperature became normal at the end of three days and he was discharged improved at the end of six days.

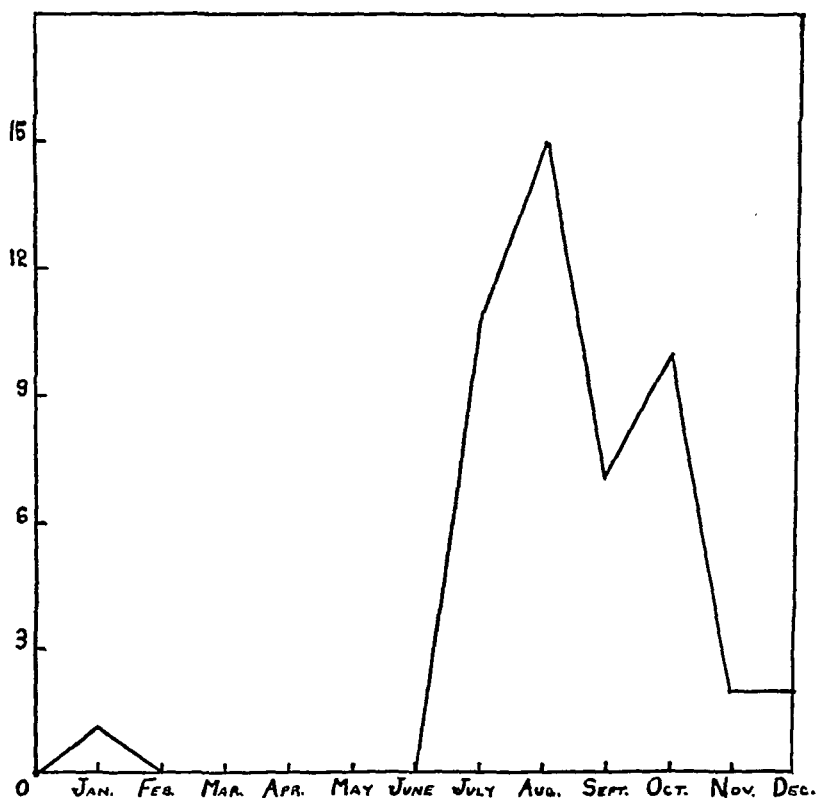


FIG. 1. Seasonal distribution of malarial coma.

Coma developed in these cases of tertian infection, presumably, as a result of toxemia. While tertian malaria is generally considered a benign disease, it is well known that it may occasionally become very malignant. It is conceivable, therefore, that coma may occur in tertian malaria in the same way it occurs in lobar pneumonia, typhoid fever and other infectious diseases.

It is possible that toxemia is also a factor in coma resulting from estivo-autumnal infections. Hegner<sup>2</sup> attributes the greater toxicity of estivo-autumnal malaria to a lack of preference of that type of parasite for reticulocytes. This obviously predisposes to a more prolific invasion of red cells.

Many tertian merozoites are killed by antibodies in the plasma or are engulfed by phagocytes while seeking a preferred reticulocyte to enter. Hingst<sup>3</sup> demonstrated by photomicrographs that the estivo-autumnal parasite is capable of undergoing direct as well as multiple division and can produce many more merozoites at the time of sporulation than any other type.

However, malarial coma is usually caused by the plugging of large numbers of cerebral capillaries by parasitized red cells. The reason estivo-autumnal plasmodia are more apt than other varieties to obstruct capillaries is ingeniously explained by Bass.<sup>4</sup> He has demonstrated that the estivo-autumnal parasite is firm in consistency and lacks ameboid movement so that it cannot change its shape to conform to the lumen of the vessels.

Coma in malaria is obviously an evidence of neglect. Malaria is very amenable to treatment and no patient adequately and fairly promptly treated should become comatose. The average duration of illness in our series when a history could be obtained was 12 days. Naturally, the disease should and could have been brought under control long before this period.

The geographical distribution of malarial infection is well known. With our modern means of transportation, however, diseases are no longer limited to certain areas. It is quite easy for an individual infected with malaria in the South to reach a distant portion of the country during the period of incubation. It is conceivable that such an individual would be more likely to become comatose under these circumstances than if he remained in the South, because physicians in non-malarial districts are not "malaria conscious" and would be more likely to overlook the cause of disease. It is the opinion of the authors that malarial coma may be more widespread than has previously been realized.

The diagnosis of malarial coma is not difficult. Fever is usually present, though not always. Some patients are in shock and have a sub-normal temperature. Thirty-nine of our 48 patients had an elevated temperature. The seasonal incidence will naturally make one think more seriously of malaria as a possible cause of coma in the late summer and fall. A history, if available, of probable exposure to malaria infested mosquitoes or of recent illness with chills and fever is of value. A lemon colored tint of the skin is often seen. Occasionally the skin will present a "muddy" discoloration which, according to Bass,<sup>5</sup> is due to phagocytosis of malaria pigment by the endothelial cells of the capillaries. The liver and spleen are enlarged in malarial infections. These organs may usually be palpated in malarial coma. Evidences of dehydration are common. Examination of the blood usually reveals a reduction in number of red blood cells and in percentage of hemoglobin. The total number of leukocytes is generally around normal in malarial infections, but the percentage of mononuclear cells is increased. In coma, however, a leukocytosis may occasionally occur. It was present in five of our cases and in these the white cells ranged from 10,450 to 30,000. Obviously, the diagnosis is definitely made by finding the parasites in the blood smear or thick drop preparation. It is usually not difficult to find the

organisms in malarial coma, because they are quite numerous by the time coma develops.

That coma is a serious complication of malaria is indicated in our series by the fact that 19 of our 48 patients died, a mortality rate of 40 per cent. The average duration of coma prior to admission in our cases in which a history could be obtained was 17 hours. Several of our fatal cases might have been saved had they received adequate treatment in an earlier stage of their coma. Coma does not develop in malaria, however, until the infection has become overwhelming. It should always be considered, therefore, with gravity.

In the treatment of malarial coma one must bear in mind that one is dealing with an emergency. A drug which is rapidly effective should be selected and it should be administered in a manner that will insure prompt action. Quinine dihydrochloride or any other water-soluble quinine compound, given intravenously, meets these requirements. The maximal initial dose of ten grains should be given to the average sized adult. Clinicians differ as to the desirable dilution for intravenous administration. Bass<sup>5</sup> recommends that it be given in 20 c.c. of normal saline. Others advise administering the drug in 250 or 300 c.c. of physiologic salt solution. The authors believe that it is not important whether the drug be given in small or large dilution, but it is most essential that it be administered very slowly. Thirty minutes should be the minimal time allowed for the introduction of the drug into the blood stream. Obviously, it is easier to give larger dilutions slowly. This may be repeated every six or eight hours until the patient regains consciousness. Except in rare instances of idiosyncrasy to quinine, no unfavorable effects should result when it is properly administered. As soon as the patient's condition permits, the intravenous administration should be discontinued and oral treatment instituted.

### SUMMARY

1. The incidence of coma on admission to the John Gaston Hospital over a period of five years was 1.4 per cent. Malaria was seventh among the diseases responsible.

2. Malarial coma is more common in the autumn and is usually a complication of estivo-autumnal infection. This type of parasite is capable of occluding the capillaries of the brain, a quality not present in other plasmodia.

3. Our series of 48 cases is unique in that three of the patients were infected with only the plasmodium vivax (tertian malarial parasite). These three cases are briefly reported.

4. Coma is a serious complication of malaria. The mortality in our series was 40 per cent.

5. This complication may be prevented by adequate, early treatment. When coma develops it is best treated by quinine administered intravenously.

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# EFFECT OF OXALIC ACID INTRAVENOUSLY ON BLOOD-COAGULATION TIME IN THREE HEMOPHILIACS \*

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THE present conception of hemophilia<sup>1</sup> is that it is a constitutional disease characterized by prolonged hemorrhage, due to increased coagulation time. There is an inherited, sex-linked defect in the clotting mechanism. The typical finding is an increased coagulation time, which apparently results from a deficient supply of thromboplastin, which is in turn due to an abnormal resistance of the platelets to disintegration.

Quick<sup>2</sup> states that if thromboplastin is added, hemophilic blood will coagulate as rapidly as normal blood. This indicates that a deficiency of thromboplastin is the probable cause of the defective clotting, and that it is probably the slow liberation of thromboplastin from the platelets, rather than the absence of any factor essential for coagulation, that is responsible for the prolonged clotting time in hemophilia. In discussion of this, Birch<sup>3</sup> states that the important question is why the platelets do not break up. One group of workers believes that the mechanical resistance of the platelets to disintegration is actually increased, while another group holds that the platelets are normal, although placed in an abnormal environment, that is, hemophilic plasma.

W. H. Howell,<sup>4</sup> in the Wesley M. Carpenter Lecture (1938), stated that recent work furnishes good evidence for the view that blood plasma contains a specific substance which accelerates the process of clotting and which is present in smaller amounts in hemophilic blood. This substance is called "plasma thromboplastin" in the plasma, and "tissue thromboplastin" in the tissues. His experiments indicate that plasma thromboplastin is present in smaller amounts in hemophilic than in normal blood.

Other research<sup>5</sup> has suggested that in hemophilia there may be a deficiency in certain serum globulins and it has shown that a globulin substance prepared from normal human serum accelerates clot formation of hemophilic and normal blood, but that hemophilic blood serum lacks this property.

The control of hemorrhage in hemophiliacs has long been one of the most difficult conditions confronting physicians. At the present time, multiple blood transfusions offer most encouragement in the treatment of internal hemorrhage. If the bleeding occurs at some site (nose, mouth, throat, rectum, etc.) that can be reached locally, the use of coagulating snake venoms (Russell's viper<sup>6</sup> and fer-de-lance) is effective.

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Timperley<sup>7</sup> and his associates, in 1936, using an extract of egg-white parenterally, reduced the coagulation time and controlled hemorrhage in cases of hemophilia. They suggested it not as a cure for hemophilia but as a means of controlling the hemorrhage itself.

Lozner and Taylor<sup>8</sup> report that dialysis of cellular-free, citrated normal human plasma yields an euglobulin precipitate containing practically all of the clot-promoting activity of the plasma for hemophilic blood. This plasma euglobulin resembles normal human plasma in its ability when injected intravenously every six hours to maintain in hemophilia a reduced level of blood-coagulation time. Other preparations, such as sheep serum, pectin, ovarian hormones, and placental extract, have been suggested as useful in reducing coagulation time.

### OXALIC ACID

In 1939, Steinberg and Brown<sup>9</sup> reported that they had prepared extracts from certain plants (shepherd's purse, wood sorrel, beets, oxalis, rhubarb, etc.) that accelerated markedly and rapidly the rate of coagulation of the blood. Subsequently, they identified oxalic acid as possessing most of the clotting power of the extract. Pure commercial oxalic acid was found to reduce the coagulation time after intravenous injection into rabbits. They established values for oxalic acid in the blood of human beings at 5.5 to 7.5 mg. per 100 c.c. Elevations in clotting time were attended by a fall in the blood oxalic acid, while reductions in clotting time conversely resulted in a rise in the oxalic-acid content of the blood.

Schumann<sup>10</sup> reports on the extensive clinical use of this oxalic-acid-containing plant extract (Koagamin) in the treatment of hemorrhage of various origins, hematemesis, bleeding gastric ulcers, jaundice, hemoptysis, hematuria, epistaxis, hemophilia, melena neonatorum and other forms of bleeding, with gratifying results. However, no case reports of its use in hemophilia are included. He states that the exact action of oxalic acid in the physiologic process of blood clotting is still problematic, but that it seems to act as a catalyzer and adds to the function of calcium, platelets, and tissue juices in the formation of thrombin.

### PHARMACOLOGY OF OXALIC ACID

Oxalic acid ( $\text{HOOC} \cdot \text{COOH} \cdot 2\text{H}_2\text{O}$ ) is a dibasic acid and is one of the strongest of the organic acids. In the blood stream, it is probably changed immediately to an oxalate of sodium or calcium.

Oxalic acid and the oxalates possess a strong acid action, resulting in local irritation and corrosion.<sup>11</sup> Intravenously, in effective doses, they produce stimulation and later paralysis. Oxalic acid is probably a constant product of metabolism and possibly one of the functions of calcium is to render it harmless. Oxalates are resistant to oxidation in the animal body.

They are excreted by the kidneys. The smallest recorded fatal dose is 5 grams.

In a recent report<sup>12</sup> it was shown that glycogenolysis in the liver is completely inhibited by amounts of oxalates equivalent to only 10 per cent of the calcium present. Precipitated calcium oxalate had no effect on glycogenolysis. According to these results, oxalate acts directly on glycogenolysis and is detoxified by precipitation with calcium. Since oxalate is present in the liver in a concentration which affects the glycogenolysis, it is probable that oxalic acid has a physiological rôle. As both the indefinite substance called "prothrombin" and fibrinogen are presumably produced in the liver, it is possible that oxalate plays a part in their formation. Steinberg and Brown<sup>9</sup> have found that elevations in clotting time were accompanied by a fall in blood oxalic acid.

### METHOD OF STUDY

As several patients with hemophilia were available, it was decided to determine the effect of oxalic acid on their blood-coagulation time. The Lee and White method for coagulation time was used because it is considered the most accurate index of coagulation of venous blood. One c.c. of venous blood, carefully drawn to prevent presence of significant amounts of tissue juice, was placed in a test tube (8 mm. in diameter), which had previously been rinsed with physiologic salt solution. The tube was gently tilted at intervals. Coagulation was assumed to be complete as soon as the tube could be inverted without displacing the clot. By this method, the normal coagulation time is 5 to 10 minutes.

The oxalic acid solution used in this study contained 1 mg. oxalic acid C.P. per c.c. of distilled water and was sterilized by autoclaving at 15 pounds pressure for 20 minutes. The solution was stored in rubber-capped vials in the refrigerator until used. As the solution was highly acid, injections were all made intravenously at a slow rate.

### CASE REPORTS

*Case 1.* R. P., a white child 11 years of age, was admitted to the Hospital on December 2, 1939, complaining of pain in the left loin, extending into the groin. This child had been known to be a hemophiliac from the time he was six months old. His 12 previous hospital admissions were for hemophilic complications, namely, uncontrollable bleeding following injury, ecchymosis, synovitis, hematuria, etc. On examination, gross blood was found in the stool. He was treated by four transfusions, 250 c.c. each. The last one was given on December 9.

On admission, his red blood cell count was 2,600,000 and hemoglobin 6 grams. The gastrointestinal hemorrhage stopped a few days after the first transfusion, and his general condition responded satisfactorily. It was decided to try oxalic acid intravenously to determine what effect it would have on the coagulation time.

Because of the patient's insistence on going home for the holidays, he was discharged on December 22, with instructions to return to the Hospital soon after the first of the year for additional studies. Nothing more was heard from him until he was admitted as an emergency patient on January 8, 1940. On the day previous to ad-

mission, he had complained of pain in the legs, increasing weakness, nausea, and vomiting. No history of trauma was obtained. The patient was in profound shock, pale and pulseless. His heart sounds were extremely faint. He died 30 minutes after admission. The patient was in such an extreme condition that oxalic acid intravenously could not be given. An autopsy was performed January 9, 1940, by Dr. W. S. Waldron.

Autopsy showed a thin, emaciated, pale boy, with ecchymotic areas on both lower extremities. The right knee was swollen, and on incision into the joint cavity, fresh, fluid blood was obtained. The peritoneal cavity contained 1,100 c.c. of fresh, fluid blood. There was a massive clot filling up the entire free space on the left side of the

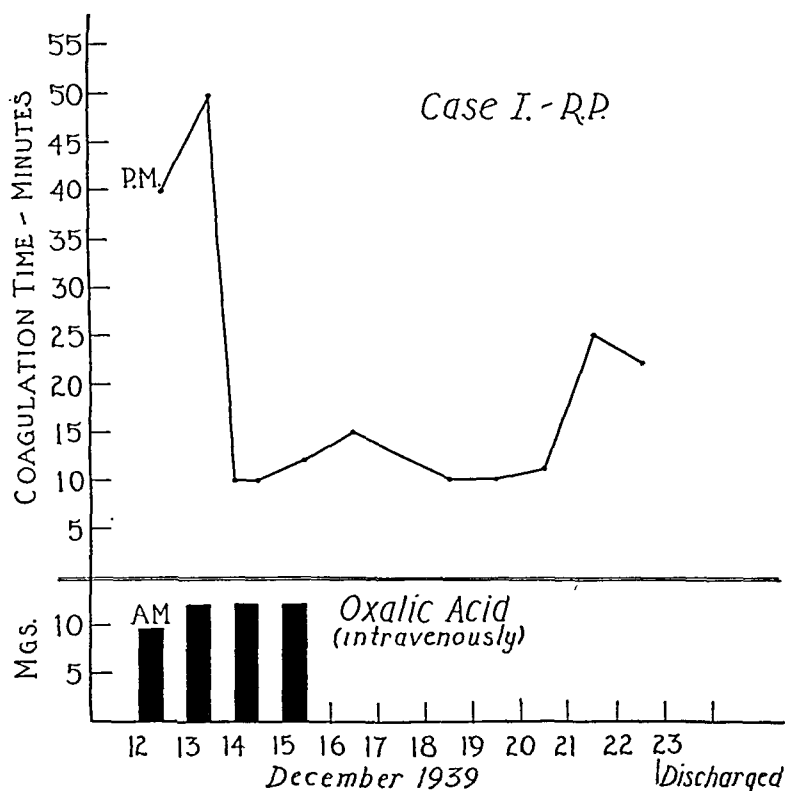


FIG. 1. Case 1. A total of 9 mg. (three injections of 3 mg. each) of oxalic acid was given on the first day (Dec. 12) beginning in the morning and the coagulation time determined in the afternoon (p.m.) was 40 minutes. On the second day after the first injection of oxalic acid the coagulation time was down to 10 minutes. The coagulation time remained between 10 and 15 minutes for one week.

Date (1939)	Coagulation Time (Minutes)	Oxalic Acid (Intraven.) mg.
12/12	40 (Afternoon)	9 (Morning)
12/13	50	12
12/14	10	12
12/15	12	12
12/16	15	
12/18	10	
12/19	10	
12/20	11	
12/21	25	
12/22	22	

abdomen and the pelvis. The clot was adherent to the descending colon, the capsule of the spleen, the left kidney, and extended into the muscular layer behind the left lumbar gutter. On further dissection, it seemed to originate from the psoas muscle, being intimately associated with the muscular fibers down to the edge of the pelvis and up to the muscular insertions in the vertebral column.

*Case 2.* J. M., male, white, 40 years old, has been a known bleeder all of his life.

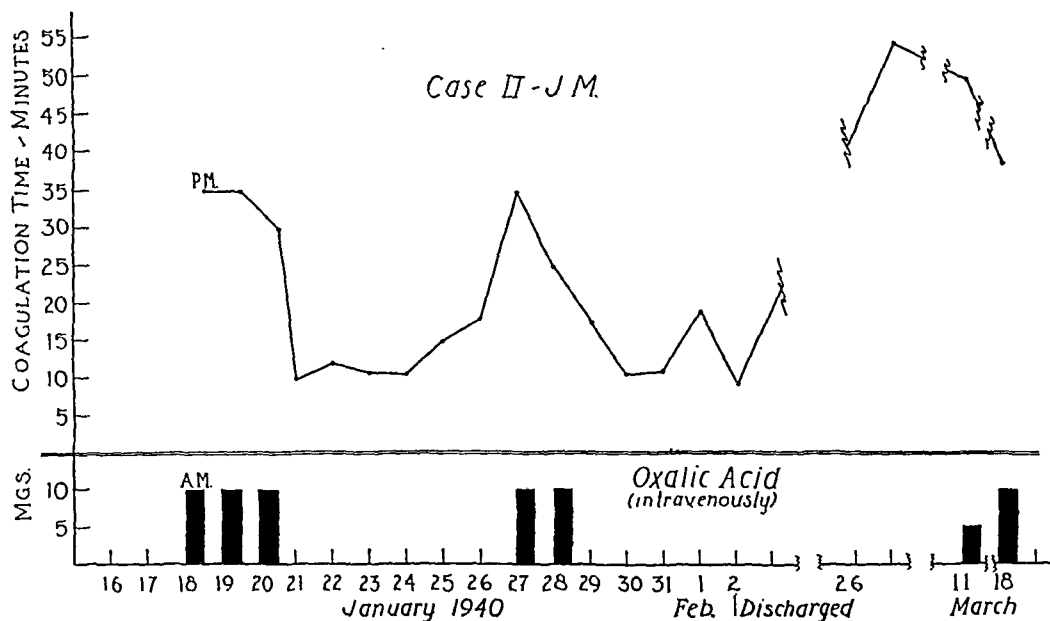


FIG. 2. Case 2. The coagulation time on admission was 50 minutes. In the afternoon, following the first morning intravenous injection of oxalic acid, the coagulation time was down to 35 minutes. On the third day following the first injection of oxalic acid the coagulation time was 10 minutes and remained less than 15 minutes for four days. Twenty-four days following his discharge from the hospital his coagulation time was 55 minutes (Feb. 26) and two weeks later (March 11) the coagulation time was 50 minutes at which time 5 mg. of oxalic acid were given. One week later (March 18) the coagulation time was 38 minutes.

Date (1940)	Coagulation Time (Minutes)	Oxalic Acid (Intraven.) mg.
1/16	50	
1/18	35 (Afternoon)	10 (Morning)
1/19	35	10
1/20	30	10
1/21	10	
1/22	11.5	
1/23	11	
1/24	16	
1/25	15	
1/26	18.5	
1/27	35	10
1/28	25	10
1/29	17.5	
1/30	11	
1/31	12	
2/1	14	
2/2	8	

He has had stiffness and swelling in his knees periodically for many years. His family history is negative except that his brother bled to death at the age of three. His previous hospital admission was on January 23, 1939, when he complained of hematuria and frequency of urination. At that admission his coagulation time (Lee-White) varied from 18 to 55 minutes, platelets were 120,000, and serum calcium was 8.8. Treatment consisted of blood transfusions.

After his discharge, he was followed by the Hematology Out-Patient Department and was given a course of sheep serum intracutaneously, with no change in the coagulation time. He was admitted to the Hospital January 15, 1940, for a course of oxalic acid intravenously to determine its effect on coagulation time.

Physical examination revealed a well-developed, well-nourished, white, adult male, with marked dental caries, and palpable liver-edge. These were the only physical abnormalities found.

Laboratory studies showed on January 16, 1940, a prothrombin time of 25 seconds (Quick's method); serum calcium 11.4; icteric index 4; blood sugar 95 mg. per cent; non-protein nitrogen 33 mg. per cent; urinalysis negative. On January 17, 1940, the bleeding time was three minutes, and clot retraction none after two hours, complete after 12 hours. On January 22, 1940, blood calcium was 11.3 mg. per cent; and three days later the non-protein nitrogen was 29 mg. per cent.

The patient was discharged from the Hospital on February 2, 1940. On subsequent return to the Hematology Out-Patient Department, February 26, 1940, the coagulation time was 55 minutes. On March 11, 1940, the coagulation time was 50 minutes, and the patient was given 5 mg. of oxalic acid intravenously. One week later (March 18) the coagulation time was 38 minutes and oxalic acid, 10 mg., was given intravenously.

*Case 3.* F. S., a white, male child, aged six, has been known to be a bleeder all of his life. He has a younger brother who is also a hemophiliac. He has been admitted to the Hospital on four occasions for hemophilic manifestations, such as hematuria, ecchymosis, and synovitis. The coagulation time during these various admissions has varied from 70 minutes to three hours. The treatment has consisted of transfusions and, following this, the coagulation time has been reduced to somewhat normal limits (on one occasion seven minutes). He was admitted to the Hospital on January 16, 1940 so that the response of his coagulation mechanism to oxalic acid intravenously might be studied.

Laboratory studies, on admission to the Hospital (January 16, 1940), showed 4,280,000 red blood cells and 12 grams of hemoglobin. There were 7,800 leukocytes, of which 58 per cent were polymorphonuclear cells, 38 per cent lymphocytes, and 4 per cent mononuclear leukocytes. The icteric index was 3; the serum calcium 11.8 mg. per cent serum; blood sugar 83 mg. per cent; and non-protein nitrogen 28 mg. per cent.

On January 17, 1940, the bleeding time was three minutes, the prothrombin time 35 seconds (Quick's method), and clot retraction, which began in two hours, was complete in 12 hours. Calcium was 10.6 mg. per cent on both January 23 and January 31, 1940.

The blood count of February 5, 1940 showed 4,350,000 red blood cells and 12.5 grams of hemoglobin. There were 6,900 leukocytes, of which 63 per cent were polymorphonuclear cells, 34 per cent lymphocytes, and 3 per cent mononuclear leukocytes. Urinalysis was negative; bleeding time was three minutes; prothrombin time 30 seconds; and clot retraction was complete in two hours.

On February 6, 1940, the blood sugar was 91 mg. per cent, and non-protein nitrogen 26 mg. per cent.

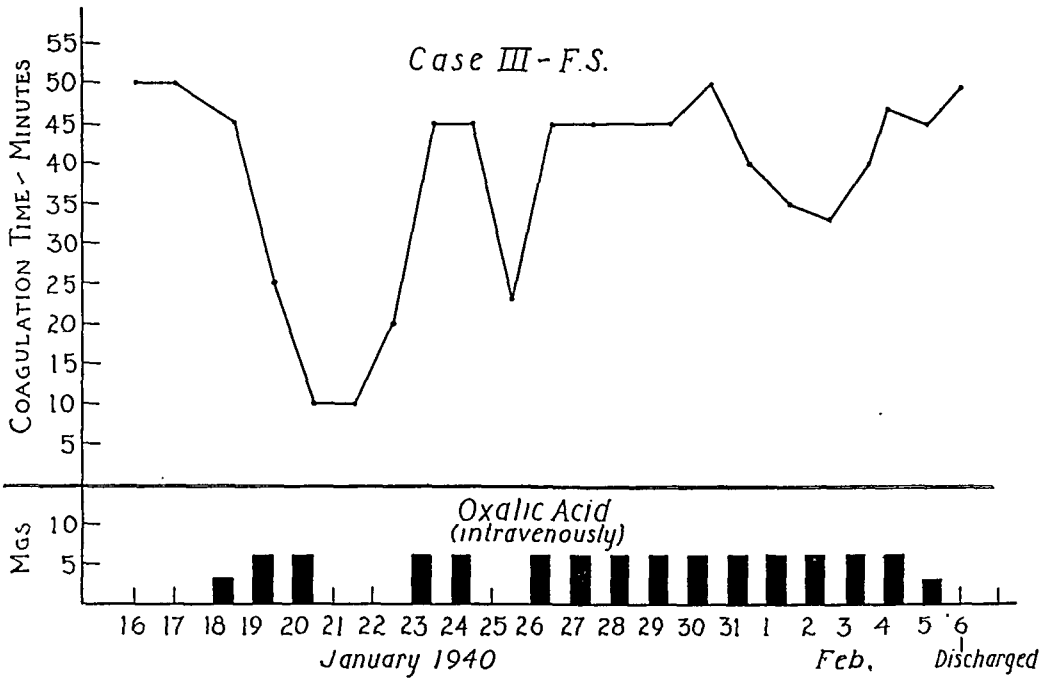


FIG. 3. Case 3. Coagulation time before oxalic acid was given was 50 minutes. On the third day of oxalic acid therapy the coagulation time had decreased to 10 minutes. After three days of no oxalic acid the coagulation time had risen to 45 minutes. Following this he was refractory to further injections of oxalic acid.

Date (1940)	Coagulation Time (Minutes)	Oxalic Acid (Intraven.) mg.
1/16	50	
1/17	50	
1/18	45 (Afternoon)	3 (Morning)
1/19	25	6
1/20	10	6
1/21	10	
1/22	20	
1/23	45	6
1/24	45	6
1/25	23	
1/26	45	6
1/27	45	6
1/28		6
1/29	45	6
1/30	50	6
1/31	40	6
2/1	35	6
2/2	33	6
2/3	40	6
2/4	47	6
2/5	45	3
2/6	50	

## DISCUSSION

The intravenous use of oxalic acid caused the coagulation time in three hemophilic patients to fall to the upper limits of normal, that is 10 minutes, in two to three days (Cases 1 and 3, two days; Case 2, three days). Oxalic acid was not given again in Cases 2 and 3 until the coagulation time had increased to 35 and 45 minutes, respectively. On resumption of oxalic-acid therapy, Case 2 responded in three days with a reduction in coagulation time to 11 minutes. On a second course of oxalic acid, Case 3 failed to respond.

There was no indication in any of the patients that oxalic acid caused toxic manifestations. The serum calcium in Case 2 remained approximately the same, while in Case 3 the serum calcium was reduced from 11.8 to 10.6 mg. after a total of 57 mg. of oxalic acid had been given over a period of 14 days.

The *modus operandi* of oxalic acid in reducing the coagulation time in hemophilia is unknown. One of the most likely possibilities is that by disturbing the physico-chemical relationship, it decreases the platelets' resistance to disintegration. The surface tension of the platelet membrane may be altered so that thromboplastic material is more readily released. The elucidation of this mechanism will undoubtedly furnish important information as to some of the controlling factors in blood coagulation.

From figures 1, 2, and 3, it is apparent that the reduction in coagulation time is quite transient, indicating that whatever is altered in the coagulation mechanism rapidly returns to its original state. The reaction in Case 3 in responding significantly to the first series of injections of oxalic acid and not to a subsequent series would indicate that the coagulation mechanism was able to compensate for the presence of oxalic acid.

## RESULTS

Limited studies on three hemophiliacs indicated that intravenous oxalic acid quickly reduced their blood-coagulation time. The rapid return to prolonged coagulation time after its administration suggests that oxalic acid does not constitute a cure for hemophilia. However, it would seem to be valuable as a measure in attempting to control bleeding in hemophilia. For this emergency therapy, oxalic acid, 5 mg., in sterile solution, can be given intravenously two to three times daily for several days.

## SUMMARY

1. Three hemophiliacs with prolonged coagulation times were given oxalic acid intravenously and their coagulation times studied.
2. The coagulation time of each decreased to normal in two or three days.
3. Oxalic acid was then stopped, following which the coagulation time increased at different rates in the three cases (Case 1, 22 minutes after seven days; Case 2, 35 minutes after six days; and Case 3, 45 minutes after three days).



4. The modus operandi of the decrease in coagulation time is not known.
5. No evidence of toxicity was present in any of the three patients who received oxalic acid intravenously.
6. There is no indication that oxalic acid can be considered as a cure for hemophilia. It would appear, nevertheless, that its use, along with other known beneficial measures, notably multiple transfusions, would be warranted in attempting to control bleeding in hemophilia.

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# THE PREVENTION OF ARTHRITIC DEFORMITIES BY EARLY ORTHOPEDIC MANAGEMENT \*

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ORTHOPEDIC surgery provides many excellent reconstructive operations for overcoming the crippling deformities of arthritis.<sup>1, 2, 3, 4</sup> Whenever the writer has had to treat a patient by an arthrodesis or the reconstruction of a joint, the need has been apparent for an effort on the part of the medical profession<sup>5, 6</sup> to prevent the deformities requiring such procedures. Thereby, patients whose vitality is already depleted by the ravages of a chronic systemic disease would be saved from submitting to major operations. The need for a concerted effort to preserve normal joint structure and function becomes more evident in view of the fact that *the average deformity in the average arthritic could have been prevented.*

Of paramount importance in the care of a patient with arthritis, if he is to be saved from a state of partial or total invalidism, is the institution of *early orthopedic management.* By early orthopedic management, the muscle strain and the traumatic joint irritation<sup>7, 8</sup> due to faulty body mechanics are overcome. By early orthopedic care, contractures are prevented, or if slight distortions are already formed, correction is established before they become fixed deformities. At the same time, orthopedic care provides for placing acute joints mechanically at rest, affording relief from pain. Orthopedic management should be instituted as soon as the diagnosis of arthritis is made,<sup>5, 9, 10</sup> and the attending physician should not wait until deformities are well advanced before he provides his patient with orthopedic help.

Sufficient emphasis is not placed on orthopedic management in the early stage of arthritis, although there is widespread appreciation of the value of orthopedic treatment late in the disease. In fact, practically everyone who has contributed to the literature on this subject has indicated the importance of orthopedic care in arthritis. Yet, with such general recognition of the value of this treatment, serious deformities (figure 1) are seen, which could have been prevented if simple orthopedic measures had been used at the onset of the illness. The statistics on the economic loss<sup>11</sup> and human suffering from arthritis<sup>12, 13</sup> are appalling, but so few are cognizant of the basic cause that no substantial effort is made to combat it. The explanation of the development of such deformities would seem to lie in the failure to appreciate the fact that orthopedic care must run *concurrently* with medical care<sup>14, 15</sup> from the time that the diagnosis of arthritis is made.

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The attitude of the attending physicians, as well as that of the patient, accounts to a certain extent for the lack of complete care of the patient suffering from arthritis.<sup>16</sup> Although there is perhaps no disease which requires the therapeutic assistance of so many branches of medical practice<sup>17</sup> as does arthritis, the burden of responsibility rests squarely and equally on the shoulders of the internist<sup>5</sup> and the orthopedist. It is their joint duty to meet the problem and cope with it to the best of their ability. The internist rightly recognizes arthritis to be primarily a medical disease belonging to his specialty, whereas the orthopedic surgeon considers joint involvement as his own domain. Both the internist and the orthopedist must realize that arthritis is not his sole possession and they must appreciate that the control of this disease calls upon their *combined effort*.



FIG. 1. (Left) Preventable deformities.  
FIG. 2. (Right) "Comfortable position" encourages deformities.

In the mind of the patient, "rheumatism" is such a common ailment that it is difficult to make him believe that early pain and swelling of one joint may be the first sign of a disease that can involve his entire body and result in total disability. The patients must be educated to realize the importance of the first signs of the disease and the necessity for prolonged treatment<sup>18</sup> by whatever special methods of therapy they individually require. The coöperation of the patient, the internist, and the orthopedist is needed in the effort to solve the problem of the treatment of arthritis.

In order to approach the subject of orthopedic management intelligently, it is necessary to have a thorough understanding of the nature of the deformities that develop in arthritis. Table 1 is self-explanatory, but it should be emphasized that deformities are not simple entities limited to a single joint; rather, deformity progresses<sup>19</sup> and one deformity leads to the development of more serious secondary, complex deformities.

When a joint is inflamed, the muscles controlling the joint contract in order to prevent not only active motion, but also that caused by the nursing

phases of the acute cases, since the hematoma forces the inner aortic layer inwards against the aortic lumen as well as it pushes the outer layer peripherally. In one of our acute cases, only a loud systolic murmur was heard in the aortic area and the absence of a diastolic murmur was noted. Necropsy revealed the unique picture of dissecting hematoma almost choking off the aortic lumen by reason of the inner bulge (figure 4). A reduc-



FIG. 4. Acute dissecting aneurysm in which the dissecting hematoma has crumpled together the inner layer of the aortic wall, seriously reducing the aortic lumen. In this case only a harsh systolic aortic murmur was heard; a diastolic murmur could not be detected. The aortic ring is not dilated and the aortic valve leaflets are normal. Small arrows indicate the outer half of the aortic wall. A large part of the dissecting hematoma has been removed. Right auricle, R.A.; Left auricle, L.A.

tion in lumen may explain the systolic phase of the double aortic murmur often heard in the acute cases. Often, however, only a diastolic murmur is heard and in chronic cases such as herein discussed the aortic ring is not compressed but is always dilated. Where a double murmur has been present, the systolic phase eventually becomes less audible and often disappears.

malaria, multiple myeloma, lymphogranuloma inguinale, hepatic cirrhosis, tuberculosis, subacute bacterial endocarditis, terminal cancer and irregularly in syphilis and in schistosomiasis japonica, trypanosomiasis Gambian, gonorrhea and dysentery.<sup>2</sup>

In view of the fact that Bing noted positive reactions in serum occurring within three hours in only 2 per cent of some 3700 specimens obtained incidental to Wassermann tests, the incidence of 19 per cent positive reactions within even two hours, encountered in the present arthritic series, is considered as higher than is to be expected if the reaction bears no relation to this class of diseases.

In general there is a tendency toward an association of the sedimentation rate and the formol-gel reaction. A rapid sedimentation rate and a rapid and marked extent of gelation occur together (chart 3). It is notable that

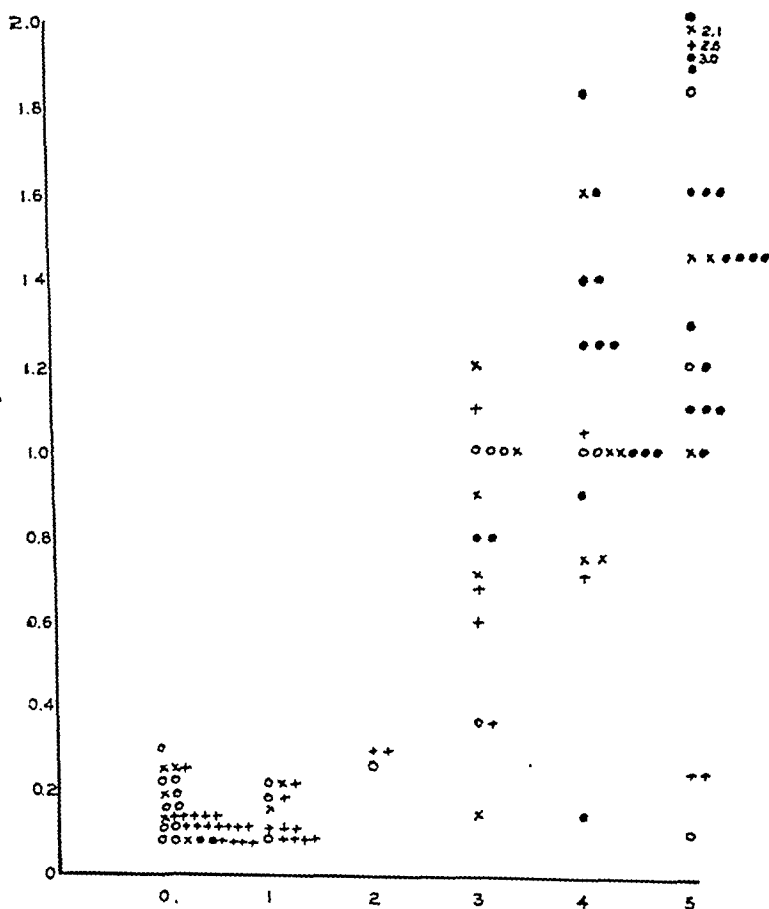


CHART 3. Relation of formol-gelation in plasma to sedimentation rate of erythrocytes in blood. Abscissae: gelation, degree at 24 hours. Ordinates: sedimentation, mm. fall per minute. Severe atrophic ●; mixed arthritic X; moderate atrophic ○; hypertrophic arthritic +.

no specimen with a sedimentation rate in excess of 0.4 fails to show positive gelation. Only seven specimens with a rate lower than 0.4 show positive

One could speculate on the disruption of some mechanism, probably of nerve control, that is concerned with the tonus of the ascending arch of the aorta. Even with small healed ruptures and dissections in the supravulvar zone, there is often notable dilatation of the aortic ring and of the ascending arch.

We found in the majority of our cases, valvular lesions of a type which does not negate in our opinion the assumption that some relaxation of the aortic ring is the basis for the murmur of aortic insufficiency. Those valvular roughenings have occasionally been seen in other cases of healed dissecting aneurysm but have been passed without comment.<sup>10,13</sup> They are almost certainly not of luetic origin. We have seen them, regardless of the etiologic factors, where the aortic or even the pulmonary valve rings have been dilated for a long time; thus they appear to be the result and not the cause of the long-continued "central" valvular leakage described above.\*

The reason for cardiac decompensation in such cases also remains somewhat obscure. No definite myocardial degeneration or inflammation was noted. It is known that aortic valvular regurgitation, while a definite handicap to circulatory efficiency, is not necessarily followed by rapid failure of the left ventricle. It is reasonable to believe, however, that most of the hearts in this small series, having already achieved their maximum in hypertrophy and efficiency in the course of hypertensive disease, were all the more vulnerable to the disturbance in hemodynamics brought on by the acute development of aortic regurgitation.

In reviewing these cases, there seems to be little information that would be of value in preventing a repetition of diagnostic error. Roentgen studies have been of definite value in the diagnosis of dissecting aneurysms,<sup>8,14</sup> but it is our impression that a positive roentgen-ray diagnosis is more likely in acute cases with a suggestive clinical background than in chronic cases seen in routine fashion and having a clinical diagnosis of aortic regurgitation and syphilis. Some of these cases will have a history of severe thoracic pain possibly two or three years previously which may engage the attention of the examiner. Two such instances which otherwise closely followed the clinical-pathological course herein reported were excluded from our series. One diagnostic feature seems worthy of further comment, namely, the high percentage of Wassermann negative cases. It is now well known that the Wassermann and Kahn tests are negative in about 30 per. cent of patients who at necropsy exhibit luetic aortitis. Such serological findings are indicative of spontaneous cure<sup>15</sup> or else of extreme latency of infection. The presence of aortic regurgitation, however, creates a different situation. A negative Wassermann reaction is very uncommon, at least in our experience, in patients with luetic aortic regurgitation, and especially so if no recent

\* With continued dilatation of the aortic ring, there is in diastole a "central" leakage of blood past the outstretched leaflets. The mid-portions of the free margins of those leaflets, occupied by the Corpora Aurantii, become roughened and eroded. Eventually, the central portions of the aortic leaflets show a replacement fibrosis.

gelation greater than 2. While this relationship is not strictly linear the grouping of values shows that correlation of rapid sedimentation rate with positive gelation is significant.

Gibson and Richardson have noted dissociation of positive reactions and sedimentation rates among rheumatic patients chiefly in gout. Bing also observed occasionally that the sedimentation rate may be elevated while the corresponding plasma may fail to give a formol-gel reaction. No dissociation of this kind was encountered in this series.

An additional factor indicating the lack of precise parallelism between the sedimentation rate and gelation on addition of formaldehyde is shown by the fact that certain *in vitro* conditions decelerating the sedimentation do not coincidentally diminish the degree of the formol-gelation. For example, bile salts, lecithin and sodium stearate added to unstable bloods reduce the sedimentation to an abnormally low rate. These materials reduce the surface tension of the plasma. However, the plasmas from these bloods react with formaldehyde to show increased viscosity. The amounts of these substances added to blood in these experiments *in vitro* exceed in magnitude the quantities likely to be present in pathological specimens. It is evident that the sedimentation of red cells is dependent not only upon the factors productive of the formol-gel reaction but also upon others.

Data on the globulin levels show that gelation tends to occur in plasmas of blood, the sera of which show elevated levels of globulin. This relationship is not linear but the trend is clear cut (chart 4). This is in accord with other studies showing that positive reactions tend to occur with high levels of globulin.<sup>2</sup> Perhaps precise correlation is not to be expected because of the lack of precision in the procedure. Gutman and Wise find the serum reaction negative after 24 hours, with sera containing less than 4.0 grams per 100 ml. Positive reactions appear in serum in 5 minutes when the globulin is greater than 5.0 grams per 100 ml.

Anemias encountered in this series generally show positive gelation. Among 40 cases with hemoglobin below 13 grams, 33 show positive reactions. Anemia *per se* does not account for the reaction inasmuch as there appears to be no constant relationship of positive gelation to the corresponding hemoglobin level.

There is no complete correlation between the leukocyte count and positive gelation with formaldehyde, although none of the bloods showing marked leukocytosis fail to show gelation. All bloods with a leukocyte level in excess of 11,000 show positive gelation.

The addition of formaldehyde to whole blood usually results in the formation of a semi-solid mass, whereas the cell-free plasma of the same blood may show a negative formol-gelation. Whether this is purely a physical or mechanical effect or due to the presence of reactive material contained in the erythrocytes is not evident. It is conceivable, however, that there may be present in the plasmas showing early and marked gelation "formed ele-

specific treatment had been instituted. A survey of our necropsy material (which thus excludes the occasional case of hypertension or of dissecting aneurysm with clinically deceptive murmurs of aortic regurgitation) reveals that positive Wassermann or Kahn reactions may be anticipated in at least 95 per cent of those patients with truly luetic aortic valvular disease. The serological reactions thus become of great importance in the diagnosis of chronic dissecting aneurysm of the aorta. Unfortunately, a few of these patients will have incidental positive serologic tests as did one of our patients and an occasional case in Wood's series.

Another clinical feature of interest was the relatively high incidence of hemoptysis in those patients who developed murmurs of aortic insufficiency. It did not occur in the other cases of dissecting aneurysm.

### SUMMARY

Occasional cases of dissecting aortic aneurysm of the chronic type closely simulate luetic cardiovascular disease. Such patients present the signs of aortic valvular regurgitation and of aortitis. Progressive cardiac decompensation may continue for many months or even years. There is often no pain and no history of a painful attack, so that if it had been present, it was relatively slight and soon forgotten. Life is terminated by heart failure, or occasionally by a long delayed secondary aortic rupture.

The aortic valvular leakage is directly dependent on the proximity of the dissection to the valvular ring. The dilatation of the latter and of the ascending arch of the aorta, in the chronic cases suggests a loss of tonus possibly secondary to the destruction of some controlling mechanism. A "mechanical" non-infectious deformity of the aortic leaflets may result from long continued inefficient closure of the aortic valve.

Notable clinical features were (1) the persistently negative serologic tests for syphilis in the large majority, (2) the usually marked and often enormous enlargement of the heart, especially of the left ventricle and the constant dilatation of the ascending arch of the aorta, (3) the relatively high incidence of hemoptysis in cases of chronic dissecting aneurysm showing signs of aortic regurgitation.

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ments" or micelles large enough to exert a physical effect on viscosity but too small to be removed by ordinary centrifugation.

The blood fluids, especially the strongly positive plasmas, in addition to showing an increase in viscosity after the addition of formalin, also exhibit an increase in scattering of light. Wise and Gutman consider it desirable to record the rate of development and the extent of this opacity as well as of the gelation. The development of opacity is regarded as due to the presence of an abnormal globulin. While our present impression is subject to possible change, it does not now appear that separate evaluation of the opacity adds

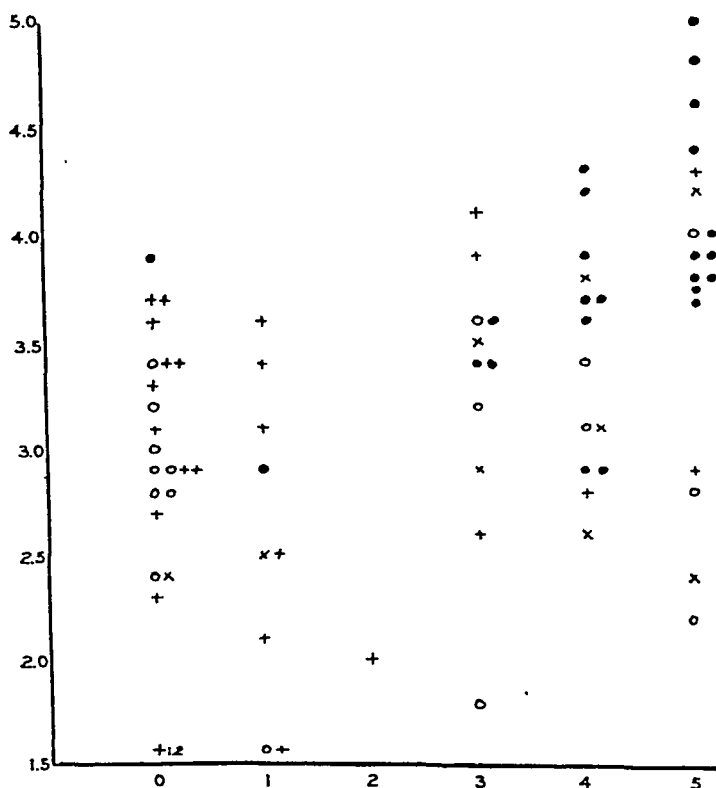


CHART 4. Relation of formol gelation in plasma to level of globulin in serum. Abscissae: gelation, extent at 24 hours. Ordinates: globulin of serum, grams per 100 ml. Severe atrophic ●; mixed arthritic ×; moderate atrophic ○; hypertrophic +.

anything to observations within the rheumatoid group. In the instances wherein positive gelation appeared in the serum there was but slight increase of light dispersion whereas the corresponding plasma exhibited a very marked increase in opacity. This suggests that the opacity factor is largely determined by the properties of fibrinogen or related substances.

The gelation of plasma upon addition of formaldehyde may be regarded as one expression of an alteration from the normal physico-chemical stability of blood, induced by pathological processes. At the possible risk of emphasizing facts which are almost self evident it may be justifiable to indicate

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that pathological plasmas which show an increase in viscosity after the addition of formaldehyde also show physical change by formation of a precipitate on the addition of salts in contrast to normal plasmas which retain their physical integrity under the same conditions. The decreased capacity of arthritic plasma to retain its fluid state on the addition of reagents, is comparable to the lessened capacity of blood from a diabetic in acidosis to withstand addition of acid without significant change in pH.

### SUMMARY

A survey of the formol-gel reaction in the blood plasma and serum of patients with rheumatoid diseases indicates that it is reasonably suitable as an index of the extent of systemic activity of the disease process. While less exact as a quantitative measurement than certain other measures, the test is sufficiently simple, and yet sensitive enough, to be employed as a routine procedure. There is a significant degree of association of the formol-gel reaction with the suspension stability of the erythrocytes. If the formol-gel reaction is negative, in the plasma, the sedimentation rate of the red cells may reasonably be presumed to be within normal limits. Bloods with positive formol-gel reactions in the plasma show in general decreased suspension stability. Positive gelation tends to occur with increased levels of globulin and with decreased levels of hemoglobin, though that last mentioned is not marked. Patients with active atrophic arthritis or mixed arthritis generally show positive reactions. Patients with hypertrophic arthritis and with moderate atrophic arthritis, while also showing positive reactions, present them in less degree and with less frequency.

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# A VALUABLE SIGN IN THE DIAGNOSIS OF FUNCTIONAL AORTIC INSUFFICIENCY \*

By SAMUEL A. LOEWENBERG, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

GARVIN<sup>1</sup> reawakened interest in the subject of functional aortic insufficiency by citing 14 cases that came to autopsy. An analysis of his cases reveals that he included in this category patients who had a diastolic aortic murmur during life, but who showed no crippling of the aortic valves at autopsy. Among this group, the majority presented definite arteriosclerotic changes and several had a double aortic murmur.

Of the 14 cases reported all but three (cases 4, 5, and 12) had high diastolic pressures: thus, case 2 had a diastolic pressure of 110; case 3, 110; case 6, 96; case 7, 90; case 8, 120; case 9, 100; case 10, 100; case 11, 138; case 13, 160; and case 14, 100. Such high diastolic pressures, irrespective of what the systolic pressures may be, certainly speak against any great degree of aortic insufficiency and should therefore suggest functional rather than organic aortic valvular defects. Considerably greater difficulty, however, is met with in the differential diagnosis between functional and organic aortic diastolic murmurs in those patients who, in addition to the diastolic aortic murmur, also show a comparatively low diastolic with a fairly high systolic pressure and visible pulsation in the superficial vessels.

We have met cases of cardiac decompensation that presented an aortic diastolic murmur, low diastolic blood pressure, visible superficial arterial pulsation and cardiac enlargement that we diagnosed as functional insufficiency. In several of these cases the systolic and diastolic blood pressures were 180/50, 160/40, 190/30 and 200/70. The diagnosis of relative aortic insufficiency was based chiefly on finding that the systolic pressure in the lower extremity equaled or was only slightly higher than in the upper extremity. The correctness of the diagnosis was subsequently proved in those who survived, by the disappearance of the murmur and the elevation of the diastolic pressure when compensation was restored. Those who died showed, at necropsy, dilatation of the aortic valve orifice, and no visible injury to the aortic valve leaflets, though in two instances there was definite loss of elasticity of one or more of the leaflets.

Normally the systolic pressure in the arm and in the thigh are about equal. When both an aortic diastolic murmur and a low diastolic blood pressure are present, one may make the diagnosis of functional aortic insufficiency if the levels of the systolic blood pressure in the arm and in the thigh are in about the same proportion as in the normal.

In organic aortic insufficiency the systolic pressure is between 50 and 100 mm. of mercury higher in the thigh than in the arm. In functional

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# OBSERVATIONS ON THE SUSCEPTIBILITY OF PNEUMOCOCCI TO SULFAPYRIDINE, SULFATHIAZOLE AND SULFA- METHYLTHIAZOLE \*

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STRAINS of pneumococci have been shown to vary in their susceptibility to the action of the same sulfonamide drugs both in vitro<sup>1-4</sup> and in therapeutic experiments in vivo.<sup>1, 5</sup> These differences in susceptibility have been noted among strains of the same type<sup>6</sup> and among different types.<sup>1-5</sup> Resistance to the action of sulfapyridine has been induced in previously susceptible strains both in vitro<sup>7</sup> and in animals experimentally infected and treated with subeffective amounts of drugs.<sup>1</sup> In this paper is presented a study of the in vitro susceptibility to sulfapyridine, sulfathiazole and sulfamethylthiazole of pneumococci isolated from patients undergoing treatment with either sulfapyridine or sulfathiazole. A study was also made of the relative susceptibility to each of these three drugs of (1) strains made resistant to any one of them and (2) strains isolated from patients after intensive treatment with either sulfapyridine or sulfathiazole.

## MATERIALS AND METHODS

*Pneumococcus Strains.* The stock strains are the same as those used in previous studies in this laboratory. Their virulence has been maintained by frequent mouse passage and they were transferred in blood broth between such passages. Strains from patients were isolated from sputum, blood or purulent exudates obtained during the acute stage of infection. Sputum strains were isolated from individual colonies of the growth on blood agar plates either of the sputum or of the heart's blood of an inoculated mouse. In each instance the freshly isolated cultures were transferred several times in blood broth and were used only after growth was obtained regularly in this medium. With some strains, particularly those of Type VII, it was difficult to obtain good growth in this medium with small inocula.

The *culture medium* used throughout this study consisted of a beef infusion broth containing 1 per cent (Bacto-) peptone and 0.05 per cent dextrose—1 per cent of defibrinated rabbit blood being added before it was distributed into individual culture tubes. Growth curves in this medium, both with and without sulfapyridine, have been presented previously.<sup>3</sup> These earlier experiments have indicated that this medium is satisfactory for comparative studies such as the ones with which we are concerned here.

*Tests for Drug Susceptibility.* Stock solutions of broth containing 60 mg. of

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

The study was carried out with the technical assistance of Mildred W. Barnes and Clare Wilcox. The chemical determinations were made by Elizabeth S. Smith and Louise Sheldon.

aortic insufficiency no such variation occurs; the systolic pressure in the thigh is about the same or only slightly higher than in the arm.

In passing, it may be recalled that in coarctation of the aorta the systolic pressure is markedly higher in the arm than in the thigh.

To obtain the blood pressure of the lower extremity, the sphygmomanometer cuff is applied to the lower portion of the thigh and the stethoscope is placed in the popliteal space, the knee being somewhat raised to allow the application of the stethoscope.

#### SUMMARY

In functional aortic insufficiency the systolic pressures in the upper and lower extremities are about equal. In organic aortic insufficiency the systolic pressure in the lower extremity is from 50 to 100 or more mm. of mercury higher than in the upper extremity.

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sulfapyridine, sulfathiazole and sulfamethylthiazole\* per 100 ml. were prepared by adding the proper amounts of the powdered drugs to the plain broth and heating in live steam for 30 minutes. By proper dilution of these stock solutions in plain broth, 14 concentrations of drug in broth were freshly prepared, the proper amount of defibrinated rabbit's blood added, and the drug-blood broth then distributed in 1 ml. amounts into 100 by 13 mm. culture tubes. The concentrations of drug used were 1, 2, 3, 4, 5, 6, 7, 8, 10, 15, 20, 30, 40 and 60 mg. per 100 ml.

A fully grown 8 to 12 hour culture was diluted serially in plain broth in such a manner as to approximate, as nearly as possible, 100 organisms in the 0.1 c.c. inoculum. The actual numbers of viable organisms inoculated were determined by pour plates. This was inoculated into each drug-blood broth tube and a blood broth tube containing no drug was always included as a control. While differences in the end points were observed with variations in the size of the inoculum of the same organisms, actual tests indicated that these differences were not significant in the range of inocula used in these tests. The occurrence of visible growth in each tube was noted after 24, 48 and 72 hours. At each of these intervals a standard loopful taken from several tubes at and beyond the endpoint of visible growth was streaked on the surface of blood agar plates. Occasionally pour plates were made from a number of the tubes beyond the ones showing full growth, as a check on the method. Repeated tests indicated that visible clouding of the medium above the sedimented red blood cells indicated a population of one million or more organisms per milliliter, and that growth on the blood agar plate failed to occur if there were less than a thousand viable organisms per milliliter. These are, therefore, the approximate limits of the test as used here. Typical tests with three strains of varying susceptibility are shown in table 1. Only the tests with sulfapyridine are presented as an illustration and, for comparison, there is included also a test of the most susceptible of the three strains after it was accommodated to grow freely in broth containing 5 mg. of sulfapyridine per 100 ml.

*Development of "Resistant" Strains in Vitro.* This was done by repeated transfers in increasing concentrations of sulfapyridine, as suggested by MacLeod.<sup>7</sup> It was found that the process could often be speeded up considerably by first growing the organism in several different concentrations of drug and, at 24-hour intervals, transferring from that tube which contained the greatest concentration of drug and showed full growth to tubes of fresh broth containing the same and progressively greater concentrations of drug. Organisms thus made resistant were transferred one or more times in broth containing no drug before they were tested for susceptibility.

Concentrations of the various drugs used were determined essentially according to the method of Bratton and Marshall.<sup>8</sup>

## RESULTS

*Comparison of Susceptibility of Pneumococci to Three Sulfonamide Compounds and the Effect of Varying the Concentration of the Drugs.* In figure 1 are shown growth curves carried out simultaneously with three different concentrations of sulfapyridine, sulfathiazole and sulfamethylthiazole. The strain used, OI, was obtained from the sputum of a patient (O'Keefe) with lobar pneumonia before treatment with sulfathiazole was begun. The patient responded well to the therapy and had a crisis 24 hours after the first dose. The same inoculum was used in each growth curve. The method of carrying out the growth curves was the same as in the studies

\*Furnished by the Lederle Laboratories, Inc., E. R. Squibb & Company and the Winthrop Chemical Company.

# THE FORMOL-GEL REACTION IN BLOOD OF PATIENTS WITH CHRONIC RHEUMATOID DISEASES \*

By C. WESLER SCULL, PH.D., and RALPH PEMBERTON, M.D., F.A.C.P.,  
*Philadelphia, Pennsylvania*

## INTRODUCTION

STUDIES conducted in this laboratory on the protein fractions in the sera of arthritics clearly show that moderate and sometimes marked hyperglobulinemia is a significant feature among certain classes of arthritic subjects.<sup>6</sup> Associated with the increase in serum globulin there is an elevation in the fibrinogen of the corresponding plasma. These results are in substantial agreement with observations made by Aldred-Brown and Monroe<sup>1</sup> and by Davis.<sup>3</sup> Recognition of the presence of these features in a given case is of practical importance, inasmuch as an elevation in the level of the globulin or fibrinogen in the blood shows the presence in the subject of clinically active processes. While hyperglobulinemia or elevation of the level of fibrinogen in itself does not reveal the specific nature of the stimulus to this end, it does demonstrate the presence of pathologically significant factors which might otherwise remain obscure or undervaluated. The procedures usually employed for the estimation of the protein moieties involve fractionation by salting out from the fluid and determination of the protein by either a colorimetric procedure or by a modification of the Kjeldahl method. These procedures are not well suited to routine use because they are unduly time-consuming and require technical skill not always available to the practitioner. In view of these considerations the possibility of employing a simple qualitative test for hyperglobulinemia encountered among rheumatic patients is regarded as desirable from the practical point of view. Among the several methods available for determination of the extent of hyperglobulinemia or hyperfibrinogenemia, the formol-gel test appears to provide desirable features of reliability and simplicity.<sup>2</sup> Since this test is not widely employed in the U. S. A. and has not been widely applied to the study of the types of chronic rheumatoid diseases encountered in American clinics, the present study was undertaken.

The formol-gel test depends upon the change in viscosity of blood fluids following the addition of formaldehyde. Several procedures based upon this property have been described. All of these are semi-quantitative and the conditions for conducting them are empirically designed. Basically, the technic consists of adding to one ml. of serum two drops of formalin (40

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From the Abington Memorial Hospital, Abington, Pa.

The expenses of this investigation were defrayed in part by a grant in memory of Alexander B. Cox.



TABLE I  
In Vitro Test for Susceptibility to Sulfapyridine of Three Strains of Pneumococci Isolated from Patients

[illegible]

per cent), or to one ml. of plasma one drop of formalin and noting the degree of gelation at convenient intervals from five minutes to twenty-four hours. Normal sera and plasmas undergo slight if any obvious physical change whereas pathological specimens containing large quantities of globulin or fibrinogen undergo a marked increase in viscosity under like conditions. The increase in viscosity may be sufficient to result in complete coagulation, i.e., irreversible gelation of the fluid.

### MATERIAL AND METHODS

The patients under observation included hospitalized and ambulatory patients from the wards and dispensary of the arthritic department of the Abington Memorial Hospital. These patients presented various kinds of rheumatoid disease of greater or lesser activity. For the present purposes 128 of the rheumatoid subjects have been classified according to the currently favored clinical criteria into atrophic, severe (38) and moderate (23); hypertrophic (44); and mixed groups (23). In view of the fact that detailed reports are available in the literature regarding the formol-gel reaction in clinical conditions other than arthritis, the present data are essentially confined to the rheumatoid class and only a few normal non-rheumatoid controls are included for comparison.

The formol-gel test has been conducted on the oxalated blood plasma of all the patients included in this series and upon the serum in one-third of the same cases. The procedure employed, though not as elaborate as some,<sup>7</sup> is essentially comparable to that used by others.<sup>4</sup> One drop (0.04 ml.) formalin (36 per cent) is added to one ml. oxalated blood plasma. Two drops (0.07 ml.) formalin are added to one ml. of blood serum. The rate of gelation is estimated by noting the viscosity on tilting the tubes at intervals of 5, 15, 60 and 120 minutes and at 18 and 24 hours. The comparative degree of gelation is estimated at each interval. Absence of change in viscosity is designated by 0. A merely perceptible increase in viscosity over that of the untreated fluid is designated as 1. A definite increase in viscosity (comparable to about (S.A.E.) No. 30 motor oil) is designated as 2; a partial gelation is recorded as 3; a fairly complete gelation, semi-solid (similar to a jelly) 4; and complete solidification showing no vibration on shaking or tapping the tube is recorded as 5.

The sedimentation rates were measured in Cutler tubes. However, for purposes of the present comparisons the relative rates are recorded in terms of the number of millimeters fall per minute at the time of the maximum drop in the level of the erythrocytes. The hemoglobin values recorded were estimated by the Haden-Houser technic in terms of grams per 100 ml. of blood. The leukocyte levels are expressed in terms of number of cells per cubic millimeter. The globulin values were determined by the Koch McMeekin micro-modification of the Howe method. The values are recorded in terms of grams globulin per 100 ml. of serum. Individual data are tabu-

TABLE I—Continued

Pneumococcus Strain	Inoculum		Hours of Growth	Cul- ture	Concentration of Sulfapyridine in mg./100 ml.												Result																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
	Dilution	Number			0	1	2	3	4	5	6	7	8	10	15	20		30	40	60																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											
S XXXIII (9)	10 <sup>-5</sup>	500	24	BB BAP	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++

Explanations:

*Pneumococcus strain.* The letter represents the patient from whom the strain was derived and the Roman numeral represents the type. P III R was derived from P III by growth in sulfapyridine (see table 2).  
*Inoculum.* 0.1 c.c. of the *dilution* was used. The *number* indicates agar plate colony count from this amount of culture.  
*Culture.* BB = blood broth growth. 0 = no visible growth; + = faint clouding with change in color of blood; ++ = full growth. BAP = surface growth on blood agar plate streaked from the BB. 0 = no growth; + = discrete colonies; ++ = confluent colonies.  
*Result.* End point (concentration of drug in mg./100 ml.) as noted in *subsequent* tables. Only the *maximum* concentration with ++ growth in BB at 48° and the *minimum* concentration with no growth on BAP at 72° are noted. See table 4: P III, C V and S XXXIII are from Cases 17, 25 and 41 (peritoneal strain), respectively.

lated in scatter diagrams to show the degree of correlation among these factors.

### DISCUSSION

Marked and early appearance of gelation is noted particularly among patients with active and severe atrophic arthritis, including spondylitis. Mild and late or delayed appearance of positive gelation is seen in the blood fluids of patients with mild atrophic and hypertrophic arthritis (chart 1). Negative reactions are seen in arrested cases of both varieties as well as among normal controls.

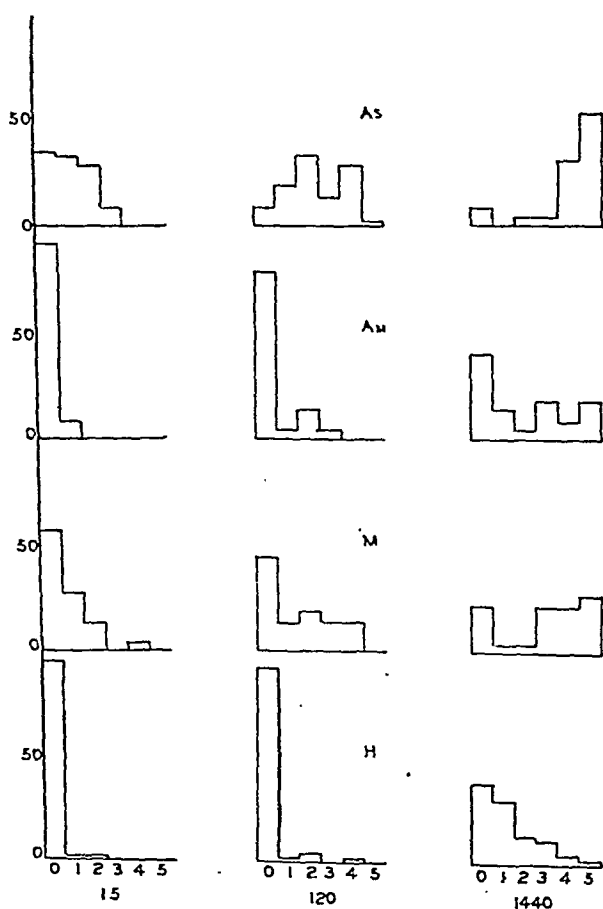


CHART 1. Frequency histogram, showing relative incidence and degree of gelation among severe (As) and moderate (Am) atrophics, mixed (M) and hypertrophic (H) arthritics. Abscissae: gelation, degree; time, minutes. Ordinates: frequency, percentage.

After the foregoing data were collected a study came to our attention by Gibson and Kersley in which positive formol-gelation reactions were found in the blood plasma of patients with rheumatoid diseases in the following order of incidence; fibrositis, 8.8 per cent; osteoarthritis (hypertrophic) 15.7 per cent; gout 20.9 per cent; arthritis with a gouty basis 33.3

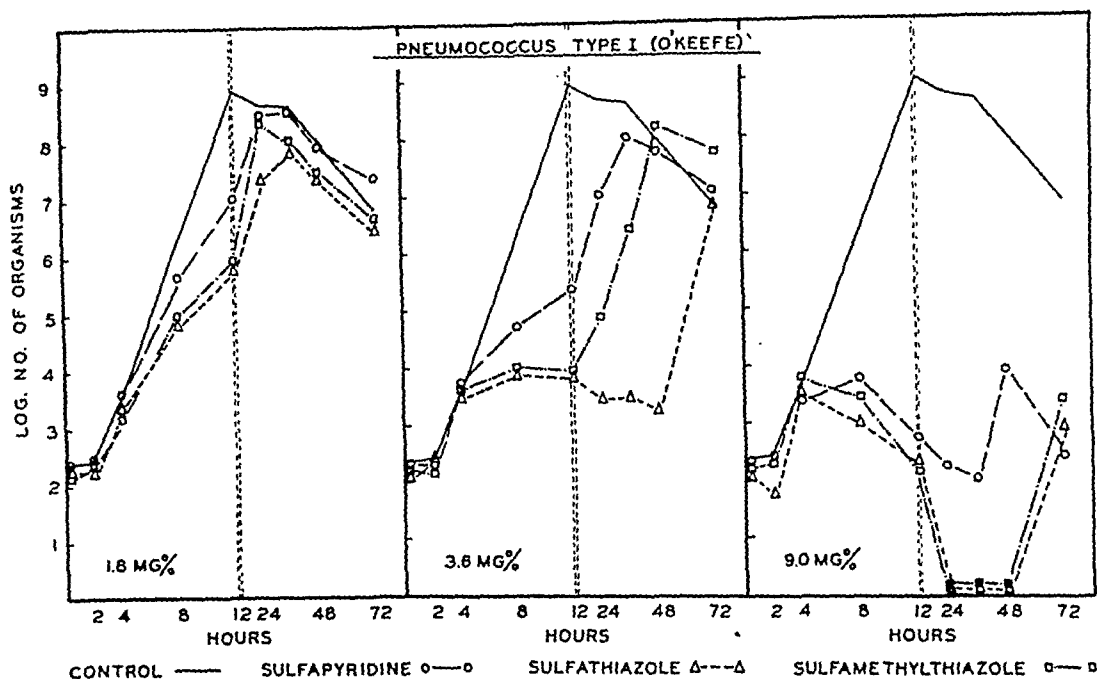


FIG. 1. Growth curves of strain OI from Case 10 carried out simultaneously with the same inoculum in blood-broth without drug and with 3 concentrations of 3 drugs.

with sulfapyridine previously reported.<sup>3</sup> The drug concentrations noted in the figure represent the amounts actually present after all the ingredients were added.

Each of the three drugs exerted a bacteriostatic effect on the growth of the organisms and this effect was greater with the high concentrations of the drugs. The comparative effect of the different drugs was more or less similar with each of the concentrations used. In general, the bacteriostatic action of sulfamethylthiazole was slightly but measurably less than that of sulfathiazole. The effect of sulfapyridine was distinctly less than that of either sulfathiazole or its methyl derivative. This same relationship did not always hold when other strains were similarly studied. In an experiment with strain P III (see tables 1 and 2), the curves with a similar small inoculum were almost identical when a concentration of 10 mg. per cent of each of the three drugs was used. In another experiment with a much larger inoculum of the stock Type III pneumococcus, 10 mg. per cent of sulfathiazole were distinctly less effective than sulfapyridine in the same concentration.

*Effect of "Drug Resistance" Induced in Vitro.* By using slowly graded and predetermined concentrations of drugs and transferring a large inoculum at 12-hour intervals, the stock Type I and Type III pneumococci, originally susceptible, were readily accommodated to grow freely in drug-broth containing sulfapyridine, 20 mg. per cent. This was determined after 60 transfers had been made in this manner. With the more rapid method previously mentioned, transfers were made each time from the highest con-

per cent; rheumatoid (atrophic) arthritis 58.3 per cent; spondylitis 88.2 per cent. These observations insofar as they are comparable are in substantial agreement with the data presented here.

Data on gelation in typically representative members of each class are shown by plotting the relative degree of gelation against the logarithm of the time in minutes (chart 2). The use of the logarithm scale for representation of time permits the illustration on the same graph of the numerically wide range of time intervals from 5 minutes to 1440 minutes.

For practical purposes it appears that observations on viscosity within the class of rheumatoid diseases need be made only at three time intervals; viz., 15 min., 120 min. and 24 hours.

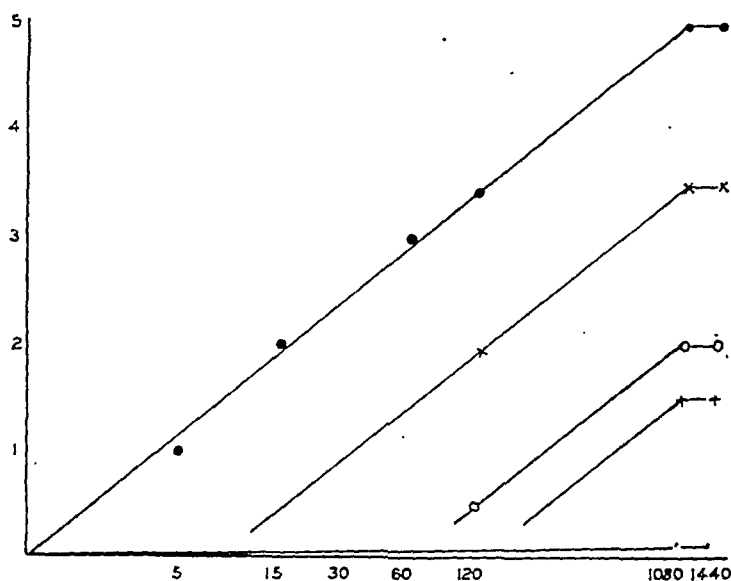


CHART 2. Rate and degree of gelation in typical cases of severe atrophic, moderate atrophic, mixed and hypertrophic arthritics and normals. Abscissae: time, logarithm minutes. Ordinates: gelation degree. Severe atrophic ●; mixed arthritic X; moderate atrophic ○; hypertrophic arthritic +; normal.

The suggestion has been advanced by Wise and Gutman<sup>7</sup> that the plasma should not be used as a test fluid inasmuch as "false positive reactions" are encountered in blood plasma while the corresponding serum reactions are negative. However, it appears that it is not only permissible but desirable to take advantage of this fact. The greater sensitivity of the plasma as an index of deviation from normal should be interpreted within proper limits and not discarded because of the existence of limitations. Within the class of rheumatic diseases the plasma is suitable for the formol-gel test since it yields positive and early reactions in those cases which are evidently clinically active and yields negative reactions in normal and less active cases. It should be noted that positive reactions have been reported in the sera of patients with a wide variety of conditions including: kala-azar, leprosy,

TABLE II

In Vitro Production of Drug Resistance by Serial Transfers in Increasing Concentrations of Three Sulfonamide Compounds

Pneumococcus Strain	Drug Used to Induce Resistance	Total No. of Transfers in Drug-broth	Concentration (mg./100 ml.) on Final Transfers	No. of Transfers in Final Concentration	Results of Tests for Resistance to 3 Drugs						
					No. of Pneumococci Inoculated	Greatest Concentration Showing Growth in BB at 48 Hours (mg./100 ml.)			Lowest Concentration Showing No Growth on BAP after 72 Hours (mg./100 ml.)		
						SP	ST	MT	SP	ST	MT
Stock I	0	0	0	—	45	1	1	1	3	3	2-7
	SP	15	5	5	300	30	15	15	>60	60	40
	ST	15	5	5	250	30	8	30	>60	>60	60
	MT	15	5	5	200	30	15	15	60	60	40
P III	0	0	0	—	57	1*	1	1	2*	2	2
	SP	15	5	7	75	20*	10	20	30*	30	30
	ST	15	5	7	36	20	20	20	40	40	60
	MT	15	5	7	85	20	20	20	40	30	30
Stock III	0	0	0	—	85	2	<1	1	4	2	3
	SP	9	5	2	200	15	15	10	20	20	20
	ST	9	5	2	150	40	30	15	60	60	40
	MT	9	5	2	150	30	10	10	>60	60	40
	SP	20	20	5	150	40	30	20	60	40	30
	ST	20	20	5	140	20	30	20	60	40	60
	MT	20	20	5	160	30	60	30	60	>60	60

\* For this protocol see table 1.

SP = sulfapyridine; ST = sulfathiazole; MT = sulfamethylthiazole.

BB = blood broth. BAP = blood agar plate.

centration of drug in which complete growth occurred into several progressively greater concentrations. By this method it was usually possible to induce marked in vitro resistance in previously susceptible strains by 8 to 10 transfers made at 24-hour intervals. Moreover, the method afforded a rough index of resistance at the time of each transfer. The drug resistance induced by either of these methods persisted essentially unchanged after numerous transfers in broth containing no drug and also after subsequent mouse passages.

Results of tests for susceptibility to sulfapyridine, sulfathiazole and sulfamethylthiazole of three strains are shown in table 2, along with the results of similar tests done after these strains were made resistant to each of these three drugs individually by the rapid method. Each of these organisms was originally highly susceptible to the action of the three drugs used so that, with the inoculum employed, free growth did not occur in concentrations of drug greater than 1 mg. per cent, and marked bacteriostasis was evident after 72 hours' growth in 4 mg. per cent or less of these drugs. In 8 to 10 transfers, these organisms had become adapted so that they grew freely from small inocula in 5 mg. per cent drug-broth. At that time, or after several further transfers in this concentration of the drugs, they grew

TABLE I  
The Common Deformities

Spine	Flexion with rotation
Shoulders	Adduction with internal rotation
Elbows	Flexion (30-40°) with pronation
Wrists	Flexion with ulnar deviation
Fingers	Flexion
	(a) Ulnar deviation
	(b) Atypical extension
Hips	Flexion and adduction—precipitating
	(a) Equinus, flexion of knee, knock knee and flat foot
	(b) Tilting pelvis
	(c) Increased lumbar lordosis
Knees	Flexion
	(a) Precipitating equinus which encourages abduction and external rotation of hip, followed by flat foot, knock knee and finally tilting of pelvis to shortened side
	(b) Posterior dislocation of tibia
Feet	Equino-Valgus
	(a) Midtarsal pronation
	(b) Depressed anterior arch
	(c) Hammer toes
Jaw	Closed

care or even by the jarring of the bed. Muscle balance is such that in practically all joints the flexor or adductor muscles are the stronger. For this reason painful joints are usually found in flexion and adduction. This is demonstrated by figure 2, which shows a patient with moderately severe rheumatoid arthritis holding his shoulders in adduction and internal rotation, his elbows flexed and pronated, and his wrists and fingers in flexion and ulnar deviation. These positions of deformity are the comfortable positions<sup>6</sup> which are assumed by the patient, and unless precautionary measures are taken the "comfortable position" leads to disaster. Several factors assist muscle contraction in the development of deformities. These include the sagging of the bed, the pressure of the bedclothes, static influences, muscle strain and gravity.

With these introductory remarks, let us see, by studying specific examples, precisely what orthopedic management means. The writer believes that if the principles to be suggested are followed, the large majority of deformities will be prevented, thereby reducing to the minimum the necessity for manipulation and open operations.

Inflamed and painful tissues demand rest.<sup>20, 21</sup> People suffering from arthritis should spend much of their time in bed.<sup>10</sup> Therefore, the patient's bed is of primary consideration. If several pillows are used under the head, the cervical and dorsal spine is forced into forward flexion. A sagging spring (figure 3) and soft mattress cause increased flexion of the dorsal spine with strain on the posterior spinal ligaments and compression of the anterior portions of the vertebral bodies and intervertebral structures. The lumbar spine becomes straight or even kyphotic, causing undue strain on the posterior spinal ligaments and the muscular and fascial supports of the back. The hips are forced into flexion, causing a contraction and shortening of the powerful ilio-psoas muscles and the Y ligaments of the joint capsules.



The knees are forced into hyperextension, causing strain on the posterior joint capsules and the posterior muscles of the thighs and calves. Such strain results in a traumatic irritation of the structures involved.

A firm bed, as shown in figure 4, is obtained by placing a one-inch thick board directly under a mattress of medium thickness. The board should extend the full length and breadth of the bed. When this firm bed is used, and one thin pillow placed under the head, and a slight support such as a folded towel or small pillow placed under the back to maintain lumbar lordosis, the strain caused by the sagging mattress is avoided. At first the patient may object to the hard bed, but he soon becomes accustomed to it

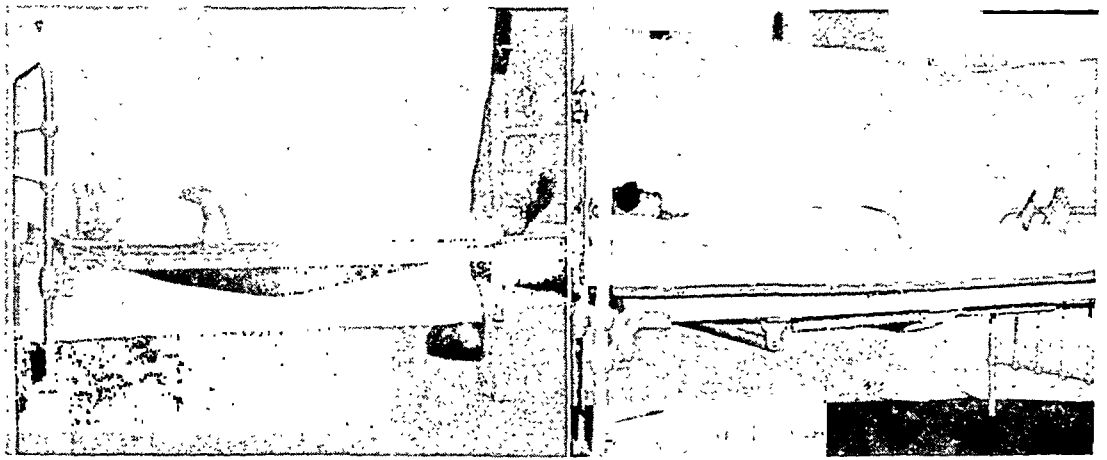


FIG. 3. (Left) Sagging bed causes deformities and soft tissue strain.

FIG. 4. (Right) Firm bed permits normal body alignment.

and finds that he is more comfortable with relief from soft tissue strain. If the patient feels the need of lateral support, pillows or sandbags may be placed along each side of the body. Patients should be discouraged from lying on their sides (shoulder and hip) as this causes severe lateral deviation of the spine. The lateral oblique position (resting on buttocks and scapula with a supporting pillow behind the back) avoids distortion and soft tissue strain and frequently affords the patient considerable rest and relaxation. (For discussion of optimum positions for function, see Timbrell Fisher<sup>22</sup> and Anopol.<sup>23</sup>)

The next important consideration is the arrangement of the bed clothing. A "cradle" is used universally to keep the pressure of blankets off painful joints, but few realize that "cradles" must also be used to prevent the pressure of bedding from holding the lower extremities in abnormal positions. The average person lying in bed allows his hips to rotate externally (figure 5), his knees to flex slightly, and his feet to go into mild equinus. If the bedding is pulled firmly over the limbs in this position, the simple distortions will advance to almost fixed deformities. The severe deformity noted in figure 6 is a result of the pressure from bedclothes, which rotated

freely in broth containing considerably greater concentrations of the homologous chemical. Furthermore, in every instance, when an organism had become resistant to the drug in which it was grown, it acquired resistance to each of the other two drugs to about the same degree. In the case of the stock Type III pneumococcus, relatively little additional change in resistance was demonstrated when, after it had become accommodated to growth in 5 mg. per cent drug-broth, it was "trained" further to grow freely in a concentration of 20 mg. per cent.

An illustration of the effect of induced resistance to growth is shown in figure 2. Growth curves in blood broth were made simultaneously with

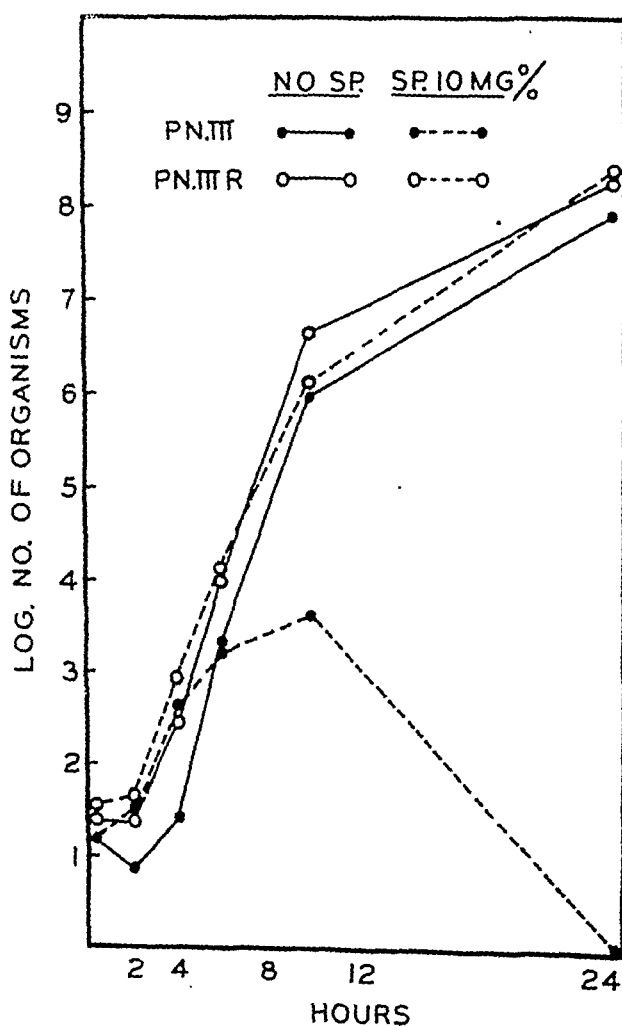


FIG. 2. Growth curves of a sulfapyridine resistant strain, III R, and of its parent Type III strain done simultaneously without sulfapyridine and with 10 mg. per cent of the drug.

the stock Type III organism and with the same strain after it had acquired resistance to sulfapyridine, as indicated in table 2. The curve of the original strain grown in 10 mg. per cent sulfapyridine shows the usual phases

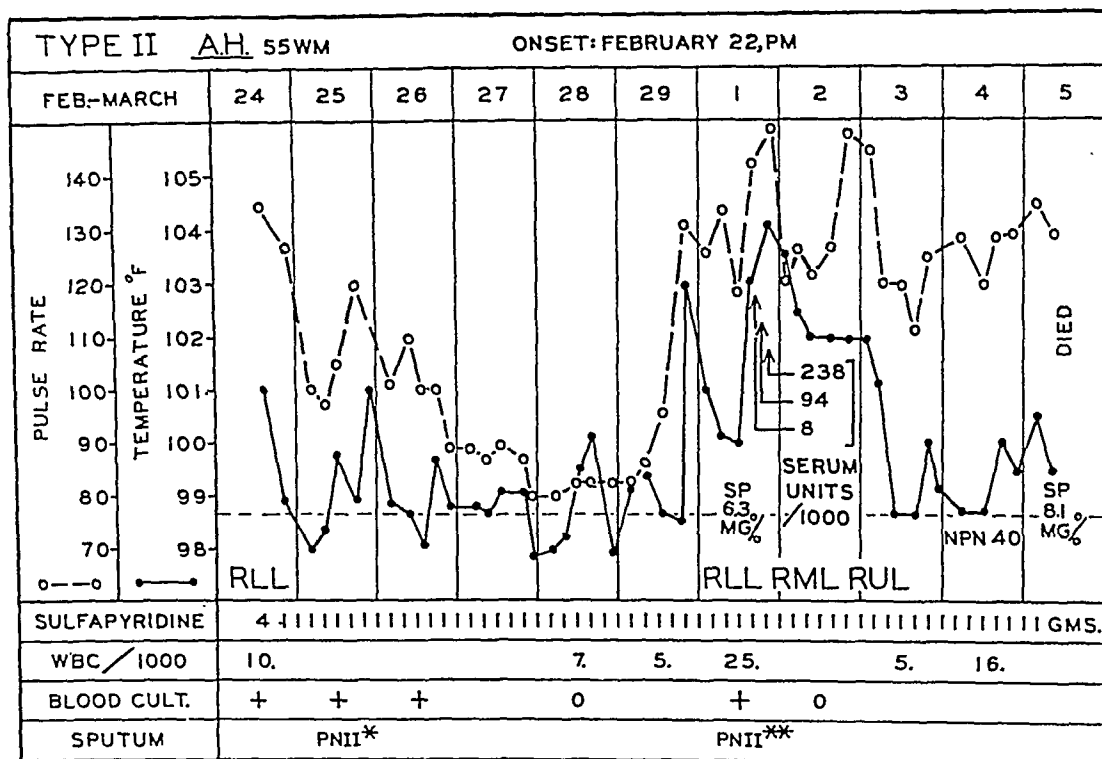


FIG. 3. Course of the disease in Case 16.

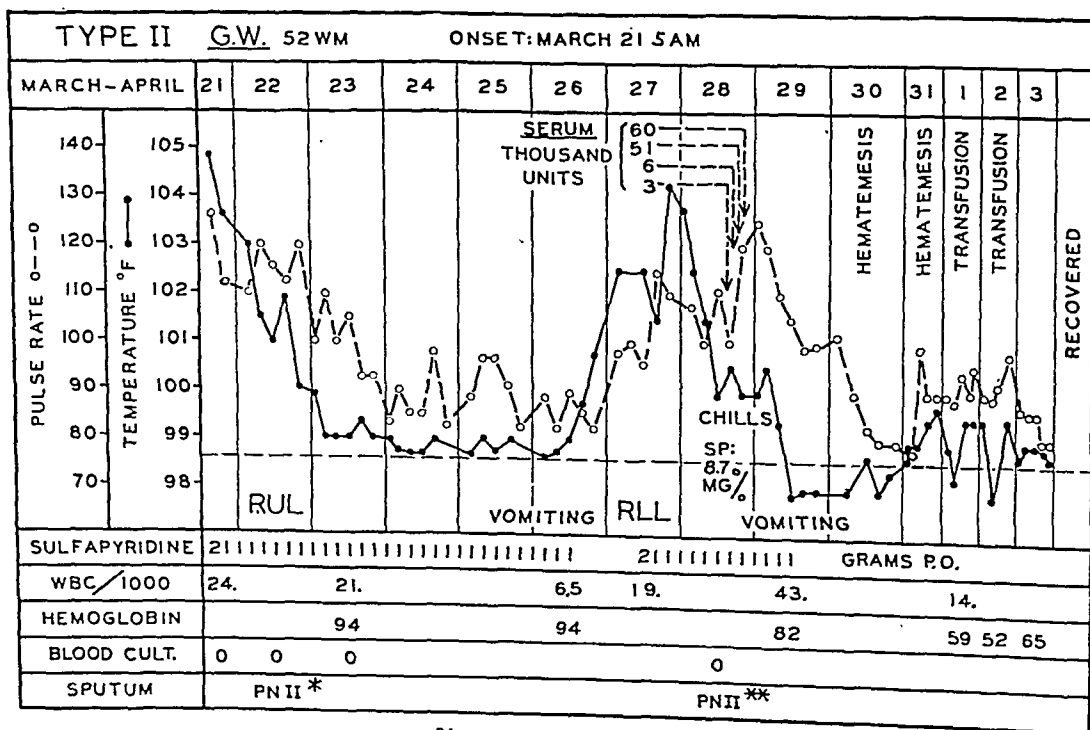


FIG. 4. Course of the disease in Case 13.

of growth, bacteriostasis and killing exhibited by a susceptible pneumococcus when a small inoculum is grown in a sufficiently high concentration of drug.<sup>3</sup> The curves of the resistant organisms made both with and without sulfapyridine, 10 mg. per cent, were identical. They corresponded essentially to the curve of the parent strain grown without drug.

While most of the strains tested could readily be made drug resistant in vitro in the manner indicated, this was not universally true. Individual strains varied in the ease with which this resistance was induced. For example, one strain, highly susceptible to sulfapyridine when first isolated, showed only a slight decrease in this susceptibility after 20 transfers in broth containing 1 mg. per cent of the drug, and this was the highest concentration in which it would grow freely. This strain was a Type III pneumococcus isolated from the spinal fluid of a patient with meningitis who died in spite of intensive treatment with sulfapyridine.\*

It was of interest to determine to what extent drug resistance may be acquired by pneumococci grown in the presence of non-bactericidal concentrations of drug without further transfers in drug-containing broth. The possibility that resistance might be induced in this manner was suggested in previous studies when growth curves in sulfapyridine-broth showed a marked decline in the viable population, which was followed by a steady increase (cf. reference 3, figure 8). A similar situation was presented in the growth curves shown in figure 1. The growth curves made with 3.6 mg. per cent of drug indicated a static population after the first 4 hours, which was followed by a marked increase in the number of viable organisms after 12 and 48 hours' growth in the sulfathiazole and sulfamethylthiazole, respectively. The curves carried out in drug concentrations of 9.0 mg. per cent were even more striking in this respect since there were hardly any colonies in the plates poured between 24 and 48 hours after the beginning of the test. A few colonies from the agar plates poured at 72 hours were, therefore, picked into blood broth and tested for susceptibility to the various drugs. The results are shown in table 3. The resistance of the organisms tested had increased to some extent in each instance. Among the organisms tested, the greatest increase in resistance was shown by the organism that had grown in 3.6 mg. per cent of sulfamethylthiazole.

#### IN VITRO SUSCEPTIBILITY OF STRAINS OF PNEUMOCOCCI ISOLATED FROM PATIENTS (TABLE 4)

*Sources of the Strains.* Tests for resistance to sulfapyridine, sulfathiazole and sulfamethylthiazole were carried out on 61 strains isolated from 45 patients with pneumococcal infections. Two or more strains were tested in 7 of the cases, these being isolated at different times and/or from different sources. A special effort was made to obtain strains from patients with typical, uncomplicated pneumonia early in the disease and before chemotherapy was started, since these offered the best opportunity to correlate the clinical response to the drugs with the results of the in vitro tests.

\* This case does not appear in the tables.



TABLE III

Change in Susceptibility of Strain OI after Growth in Drug-Broth for 72 Hours

Time of Test	Grown in		Results of Tests for Resistance to 3 Compounds						
	Drug	Mg. per 100 ml.	No. of Organisms Inoculated	Greatest Concentration Showing Growth in BB at 48 Hours (mg./100 ml.)			Lowest Concentration Showing No Growth in BAP after 72 Hours (mg./100 ml.)		
				SP	ST	MT	SP	ST	MT
Before	0	0	130	4	1	2	8	4	5
After 72 hours' growth	0	0	130	4	1	2	5	3	4
	SP	9.0	110	3	1	1	10	6	6
	ST	3.6	18	6	4	3	10	7	7
	MT	3.6	200	15	3	3	20	8	10
	MT	9.0	170	2	1	2	10	5	10

(See figure 1.)

In this category there were 23 cases (numbers 1, 3 to 7, 13 to 18, 23 to 29, 31, 32, 37 and 40). The remaining 22 cases included: 11 in whom either the treatment was begun late or there was some local or systemic complication (numbers 8 to 12, 20, 21, 30, 33, 34 and 36); 2 in whom treatment was begun early but the strains tested were obtained later during the course of treatment; 5 with focal infections (numbers 19, 22, 38, 39 and 41); and 4 with Type XXXIII<sup>9</sup> strains which were included only for comparison with the strain from Case 41.

*Susceptibility of Strains Obtained before Treatment.* Almost all of these strains were found to be susceptible to the action of the three drugs tested, as evidenced by the fact that free growth, under the conditions of the test, was inhibited by small concentrations of these chemicals. Only three of the strains (from Cases 41, 44 and 45) were sufficiently resistant to one or more of the drugs so that free growth, as indicated by visible clouding of the broth cultures at 48 hours, occurred in the presence of 5 mg. per cent or more of drug. Ten additional strains isolated before chemotherapy was instituted required a concentration of 6 mg. per cent or greater to maintain the bacterial population in the culture below the point where growth on agar plates occurred from transfers made at 72 hours. The latter may be considered relatively resistant strains.

The *inoculum* used, as indicated by plate counts, usually varied between 30 and 300 viable organisms, only occasionally falling outside these limits. In Case 21, the results of tests carried out simultaneously with three different inocula of the same strain are shown. The results with the inoculum of 33 organisms were essentially the same as with 330 organisms. The inoculum of 3300 organisms required significantly greater concentrations of drug to inhibit growth to the same extent. A second test done with a large inoculum similar to the last but carried out at another time gave the same result. Similar results were obtained with different inocula of the stock Type III strain.

## DISCUSSION

Throughout this paper the terms "susceptibility" and "resistance" have been applied rather loosely to express the relative facility with which inhibition of growth takes place in a favorable culture medium containing graded concentrations of effective chemotherapeutic drugs. Except as applied to the strains adapted artificially to growth in the presence of these drugs, the terms express only a relative ability of strains to grow in comparatively small concentrations of the drugs. With the exception of the Type XXXIII organisms from Case 41, the growth of all of the strains isolated from patients was markedly inhibited by relatively small amounts of the drugs in the media used.

The test for this so-called "susceptibility" or "resistance" as used here is, of course, rather crude. The many factors involved in the growth of pneumococci in artificial media and the variations exhibited by different types and strains, especially when first isolated, are well known. The test is, therefore, only a comparison of such growth after some degree of adaptation to the non-drug containing artificial medium used. This medium itself probably contains many factors, some known and many unknown, which may interfere to varying degrees with the growth in the media itself as well as with the action of the drugs. The results of the tests, therefore, reflect only the sum total of these artificial influences on the organisms. While the test is not altogether a satisfactory one, we have not as yet found a simpler *in vitro* test that is more satisfactory. The use of benzidine-blood agar, as suggested by MacLeod,<sup>10</sup> has not been successful in our hands, even for the detection of the most resistant strains, including those made resistant artificially.

The interpretation of susceptibility or resistance, as judged by the results of these tests, in terms of the actual infection of a living host by the given strain on the one hand, and the response of the infection to treatment with the corresponding drug, on the other, is justifiable only in so far as this can be or has been actually demonstrated under strictly controlled conditions. The strict correlation is feasible only in experimental infections in animals, and even there the essential factors can be controlled only with great difficulty. With human infections the correlation is extremely difficult because of the numerous factors in the host and in the invading organism which are involved in the processes of recovery, in addition to factors introduced by the drug itself.

It was not possible to test all the strains encountered in the clinical cases. Those chosen for the tests were obtained, in general, from two kinds of cases: (1) those with early uncomplicated pneumonia and (2) those in whom the clinical course or the response to the drug offered the possibility of finding some correlation. It is of interest, in view of the generally favorable response of the early cases to drug therapy, that all the strains isolated before treatment were highly susceptible to these drugs. In almost

TABLE IV

Results of in Vitro Tests for Susceptibility to Sulfapyridine, Sulfathiazole and Sulfamethylthiazole of Pneumococcus Strains Isolated from Patients with Active Infections and the Relation of These Results to the Clinical Course and to the Response to Treatment with Sulfapyridine or Sulfathiazole

Result of Test for Susceptibility										Remarks							
No.	Sex and Age	Pneumo- coccus Type	Day Treat- ment Began	Blood Cul- ture Before Treat- ment	Drug Ther- apy	Hours of Treat- ment Before Crisis or Death	Blood Level	Day Strain Iso- lated	Source		Inoc- ulum	Highest Concent- ration Giving Visible Growth in BB at 48 Hours (mg./100 ml.)			Lowest Concen- tration Yielding No Growth in BAP after 72 Hours (mg./100 ml.)		
												SP	ST	MT	SP	ST	MT
1	M23	I	1	+	ST	46	3.7	1	Blood	127	1	1	1	4	5	5	Serum given. See figure 5.
2	F14	I	2	0	SP	84	4.0	5	Sputum	14	7	7	10	30	20	30	
3	M49	I	3	0	ST	32	2.7	3	Sputum	57	1	1	1	5	4	4	
4	F22	I	3	+	ST	11	5.4	3	Sputum	400	1	<1	<1	3	2	2	Serum given later.
5	M22	I	3	0	ST	28	6.4	3	Throat	100	4	2	1	10	8	8	
6	M43	I	3	0	ST	80	—	3	Sputum	125	1	<1	2	2	2	3	
7	F60	I	3	0	SP	30	12.7	3	Sputum	115	2	1	1	6	3	4	Serum given.
8	M15	I	4	0	ST	34	3.5	4	Sputum	200	<1	<1	<1	2	2	1	
9	M43	I	4	0	ST	36	4.0	4	Sputum	27	1	1	<1	5	4	1	Pn. I pneumonia; blood culture +; treated with sulfapyridine 10 weeks previously. See figure 1 and table 3.
10	M33	I	5	+	ST	24	2.0	5	Blood	85	4	2	2	8	4	5	
11	M44	I	10	+	ST	36D	6.5	10	Blood	12	4	1	1	5	2	3	Rheumatic heart disease; serum given.
12	M36	I	?	0	SP	168D	10.0	?	Sputum	80	2	1	1	5	3	4	
13	M52	II	1	0	SP	36	—	1	Sputum	550	2	1	1	2	2	2	Serum given. Relapse. See figure 3.
14	M20	II	1	0	SP	37	8.7	8	Sputum	350	10	10	8	20	15	20	
15	F14	II	2	0	ST	3	3.1	1	Sputum	150	1	1	1	2	2	2	? Spontaneous crisis.
16	M55	II	2	+	SP	D. 10 days	5.3	2	Sputum	41	1	1	1	2	2	2	
							—	2	Blood	57	2	1	1	4	2	3	Serum given. See figure 4.
							6.3 8.1	8 A A	Sputum Pleura Lung	120 68 127	20 15+ 7	10 — —	8 — —	30 >15 10	40 — —	30 — —	
17	F35	III	1	0	SP	11	4.8	1	Sputum	57	1	1	1	2	2	2	See tables 1 and 2.



every instance growth was markedly inhibited by concentrations readily maintained by the patient in the course of treatment. In view of the additional fact that most patients have some degree of natural antibody to the infecting organism early in the course of pneumonia,<sup>11, 12</sup> and because of the now well known synergistic action of these drugs and specific antibody,<sup>1-4, 13</sup> it is not surprising that favorable responses to these drugs are so constant. Within certain limits, differences in susceptibility may readily be offset by variations in immunity, thus obscuring any strict correlation that may exist between susceptibility of the organism to drugs and clinical response of the patient. The fact that the strains from some patients whose response to chemotherapy was not optimum showed relatively less susceptibility to the drugs in the tests may, therefore, be significant. On the other hand, it should be noted that no early cases of uncomplicated pneumonia were encountered in whom the organisms isolated before treatment were highly resistant.

The factors underlying the variations in the response of different strains or types to the bacteriostatic action of the drugs were not studied. The fact that the Type XXXIII strains as a group were the most resistant of the organisms isolated from patients before the administration of drugs is of interest in this regard. At least four of these strains grew poorly or not at all under strictly aerobic conditions when they were first isolated. They had become gradually adapted to aerobic growth in the fluid media and on the surface of blood agar plates by the time the tests were carried out.

Of special interest are the strains isolated from patients after they had been treated with sulfonamide drugs, particularly when pneumococci of the same type, isolated before the beginning of the chemotherapy, were available for comparison. The results of the tests with these strains indicate that the *in vitro* resistance of pneumococci may be increased in the patient by chemotherapy, just as it is induced in the culture tube by exposure to the drugs. This alteration in susceptibility of the strains was consistent with the observed clinical course of the disease in the patients from whom such organisms were isolated, as illustrated in Cases 13 and 15 and in figures 3 and 4 (cf. Ross<sup>16</sup>).

Several points should be made in this regard. (1) Not all patients whose clinical response to treatment was unfavorable showed such changes in the *in vitro* susceptibility. This is illustrated in Case 38. (2) It is not certain whether such changes may not occur in patients who have an altogether favorable response. This aspect was not investigated, partly because of the great difficulty of isolating pneumococci from such patients after chemotherapy with effective drugs. This difficulty was encountered even in a number of patients who had a definite relapse of the pulmonary infection with spread of the lesion. (3) A poor response to chemotherapy may be associated with systemic complications in the patient. Some of these complications may be adversely affected by the treatment or may interfere

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TABLE IV—Continued

Result of Test for Susceptibility																	
No.	Sex and Age	Pneumococcus Type	Day Treatment Begun	Blood Culture Before Treatment	Drug Therapy	Hours of Treatment Before Crisis or Death	Blood Level	Day Strain Isolated	Source	Inoculum	Highest Concentration Giving Visible Growth in BB at 48 Hours (mg./100 ml.)			Lowest Concentration Yielding No Growth in BAP after 72 Hours (mg./100 ml.)			Remarks
											SP	ST	MT	SP	ST	MT	
18	M45	III	1	0	ST	53	7.1	1	Sputum	123	2	1	<1	3	5	1	Serum given. Otitic meningitis.
19	M75	III	3	0	ST	28D	6.4	3	Spinal fluid	250	<1	<1	<1	1	1	1	
20	M55	III	4	0	ST	25	5.6	4	Sputum	100	<1	<1	<1	1	1	1	
21	M61	III	4	0	ST	41	4.2	4	Sputum	330 3300 3000	4 5 7 8	3 3 5 7	3 4 6 7	5 7 15 15	4 4 7 8	7 10 10	
22	M25	III	?	+	SP	D. 15 days	6.4 10.7	?	Blood Spinal fluid Blood	160 160 170	4 15 3	1 10 3	3 8 2	7 30 10	4 30 6	6 10	Lateral sinus thrombosis; serum given; improved, then relapsed 3 days after drug was stopped (10th day of treatment). Bacteremia recurred with meningitis.
23	M25	IV	1	0	ST	11	4.3	1	Sputum	350	2	<1	<1	3	1	2	See table 1.
24	M52	IV	2	0	ST	20	4.1	2	Sputum	224	<1	<1	1	1	1	2	
25	F13	V	1	0	SP	21	6.0	1	Sputum	300	4	3	3	7	5	8	
26	F55	V	2	0	ST	25	5.6	2	Sputum	260	4	2	2	8	4	6	
27	F65	V	2	0	ST	12	8.3	2	Sputum	500	4	3	1	7	4	4	Serum given.
28	M25	V	2	0	ST	15	4.8	2	Sputum	143	4	2	2	3	5	3	
29	M50	V	2	0	ST	17	10.1	5	Sputum	180	2	1	2	4	4	4	
30	F44	V	2	0	ST	18	—	2	Blood	39	3	2	2	5	5	4	
31	F23	VII	1	+	ST	35	9.3	2	Sputum	400	<1	<1	<1	1	1	1	Serum given. BC+ during 5 days of sulfathiazole therapy; negative after serum.
32	M18	VII	2	+	ST	48D	8.1	7	Blood	100	1	1	1	6	6	4	
33	M68	VII	7	+	ST	180D	23.3	3	Blood	25 12	1 1	1 1	1 1	1 1	1 1	4	
34	M50	VII	3	+	ST	108	8.2	7	Sputum	200	2	1	1	5	3	4	
35	M32	VIII	3	0	SP	108	—	—	—	—	—	—	—	—	—	—	

with the proper action of the drugs. Since such complications are most frequent in very old individuals, it is not surprising that the results of chemotherapy in this group are not so striking as among younger patients. (4) Other factors may affect chemotherapeutic activity directly. High temperatures, for example, may influence the action of the drugs.<sup>14</sup>

It may be worth noting that response to serotherapy is essentially independent of chemotherapy except as it is enhanced by the latter. Poor responses to serum, where drugs fail, are usually due to the same causes as the failure of serum alone. Chief among these causes are delayed treatment and complicating systemic disease. This should be borne in mind in the interpretation of failures from combined therapy.

For most of the strains of pneumococci tested, the results indicated that the three drugs used were equally effective, weight for weight. In a considerable number of the strains tested, however, the same degree of growth inhibition was produced by smaller concentrations of sulfathiazole than of sulfapyridine. Likewise, with the same concentrations of drugs, sulfathiazole usually exhibited measurably greater bacteriostatic action than sulfapyridine, as illustrated in figure 1. At the moment, sulfathiazole has not yet been used extensively enough to warrant final conclusions as to its efficacy in the treatment of pneumococcal infections as compared with sulfapyridine. Indeed, some differences of opinion have been expressed on this point. Several clinical reports, however, suggest that, aside from the factors of toxicity, sulfathiazole may be slightly more effective than sulfapyridine in the treatment of pneumonia.<sup>15</sup>

The studies on the production of resistance by in vitro methods are of interest in certain respects. Significant is the fact that the resistance induced by growth in any one of the three drugs used was associated with resistance to the other two drugs, and usually to the same degree. This corresponded with the findings in those patients from whom relatively resistant strains were isolated after treatment with one of the drugs. These strains showed similar changes in resistance to the homologous drug and to the two other chemicals used in the tests. The three drugs tested are the only ones which, at the time of this writing, have been shown to have definite therapeutic value in the treatment of pneumococcal infections. The clinical implication would naturally be that any failure of therapy with one of these drugs, arising purely out of the resistance of the infecting organism to the particular drug that is used, would probably not be remedied by changing to either of the other two drugs. Whether or not this is actually true awaits further critical observations.

#### SUMMARY

1. The susceptibility or resistance of pneumococci to the bacteriostatic action of sulfapyridine, sulfathiazole and sulfamethylthiazole was tested in vitro by the ability of various strains to grow in a favorable medium containing graded concentrations of these drugs.

TABLE IV—Continued

Result of Test for Susceptibility										Remarks						
Sex and Age	Pneumo- and coccus Type	Day Treatment Begun	Blood Culture Before Treatment	Drug Therapy	Hours of Treatment Before Crisis or Death	Blood Level	Day Strain Isolated	Source	Inoculum		Highest Concentration Giving Visible Growth in BB at 48 Hours (mg./100 ml.)			Lowest Concentration Yielding No Growth in BAP after 72 Hours (mg./100 ml.)		
											SP	ST	MT	SP	ST	MT
36 M36	VIII	5	+	ST	35	3.8	5	Blood	250	2	2	2	5	3	3	
37 M23	XII	1	0	ST	5	5.0	1	Sputum	90	<1	<1	<1	2	1	1	
38 M50	XII	?	+	SP	D. 17 days	— 4.9* 14.9* 15.8*	? +7 +12 +15	Spinal fluid Spinal fluid Spinal fluid Spinal fluid	200 175 175 300	<1 <1 <1 <1	<1 <1 <1 <1	<1 <1 <1 <1	2 1 1 1	1 1 1 1	1 1 1 1	Serum given. *Levels are those of spinal fluid from which organisms were cultured.
39 F56	XII	4	+	SP	D. 8 days	— 8.6* 11.9* 14.2*	4 4 5 9	Blood Spinal fluid Spinal fluid Spinal fluid	24 23 138 42 85	<1 <1 1 <1	<1 <1 <1 <1	<1 <1 <1 <1	2 2 3 2 3	1 1 2 1 2	2 2 2 2 2	Serum given. *Levels are those of spinal fluid from which organism was obtained.
40 M38	XXII	3	0	ST	30	3.7	3	Sputum	500	4	2	3	8	4	6	
41 M17	XXXIII (9)	3	+	SP	D. 22 days	—	3 4 A	Peritoneum Blood Abscess	500 500 154	60+ 8 20	60+ 5 40	60+ 5 60+	>60 15 30	>60 10 60	>60 15 >60	Serum given. See table 1. Nephrosis, peritonitis and abdominal abscess.
42 M62	XXXIII	3	0	0	—	—	3	Sputum	180	2	1	1	3	3	2	Mild bronchopneumonia.
43 *	XXXIII	—	+	SP	D.	—	—	Blood	60	1	<1	2	7	2	5	*Strain from Dr. Brown. Serum given.
44 M8	XXXIII	—	+	*	D.	—	—	Spinal fluid	600	8	4	8	15	15	15	*Sulfanilamide treated meningitis (1938).
45 *	XXXIII	—	—	—	—	—	—	Sputum	400	6	3	3	15	7	7	**"Wilder" strain from Miss A. Walter. <sup>9</sup>

**Explanations:**

In 2 cases (Numbers 2 and 35) the only organism tested was isolated during drug therapy. Four of the Type XXXIII strains (Numbers 42 to 45, inclusive) are included only for comparison with the resistant strains from Case 41.

*Drug therapy:* SP = sulfapyridine, ST = sulfathiazole. Serum was given to some patients, as noted under "Remarks."

*Hours of treatment, etc.:* D = died. Others recovered. Numbers represent hours to time temperature dropped below 100° F.

*Blood levels:* Unconjugated drug, mg./100 ml. at about the time of crisis. Where more than one strain was isolated, levels given were obtained at about the time the strains were isolated.

*Day treatment begun and Day strain isolated* = number of days from onset of disease. A = autopsy.

*Inoculum:* Number of pneumococci grown in the various drug concentrations as determined by agar pour plates made at the beginning of the test. MT = sulfamethylthiazole. Except where otherwise noted under "Remarks," the patients had typical lobar pneumonia.

2. Strains of pneumococci initially susceptible to the bacteriostatic action of these three drugs were made resistant by growth in media containing increasing concentrations of these drugs. Strains accommodated in this manner to growth in one of the drugs not only acquired resistance of a high degree to the action of the homologous drug, but also became resistant to the other two chemicals to approximately the same extent. Individual strains varied in the ease with which "fastness" was acquired in this manner.

3. Some increase in drug resistance of pneumococci was noted after 72 hours' growth in bacteriostatic concentrations of these chemicals and without further exposure to them. Under such circumstances the increase in resistance may be greater when a small concentration of drug is used.

4. Strains of pneumococci isolated from patients with pneumonia or with purulent infections before treatment with drugs was started almost all showed a high degree of susceptibility to sulfapyridine, sulfathiazole and sulfamethylthiazole *in vitro*. Concentrations of drug well within the range that can be maintained therapeutically usually induced marked inhibition of growth in these strains in otherwise favorable media.

5. Individual strains varied with respect to the concentration of drugs necessary to produce the same degree of bacteriostasis. The different types also appeared to vary in the frequency with which relatively resistant strains were encountered, but the numbers of strains and types treated were too few to make definite comparisons. The greatest resistance was found among the Type XXXIII strains. Lesser degrees of susceptibility appeared to be more frequent among the Type III and Type V strains than among those of the other common types.

6. In general, most of the strains showed the same degree of growth inhibition with approximately equal concentrations of each of the three drugs used in the tests. A considerable number of strains, however, were somewhat more susceptible to sulfathiazole than to sulfapyridine, according to the results of these tests. The greater bacteriostatic action of sulfathiazole as compared with sulfapyridine was also confirmed by growth curves. Differences between the susceptibility of strains to sulfathiazole and to sulfamethylthiazole were smaller, less frequent and more irregular.

7. Strains isolated from three patients after several days of drug therapy and during a relapse of the pulmonary infection were found to be relatively resistant to the drugs. In the two of these three cases from which pneumococci of the same type isolated before the beginning of drug therapy were available for testing, these pneumococci were found to be highly susceptible. The latter strains were equally resistant to sulfapyridine, the drug with which they were treated, and to sulfathiazole and sulfamethylthiazole. In some other patients who failed to respond to chemotherapy, however, no change in the susceptibility of the pneumococci could be demonstrated.

8. Various factors concerning the methods and the interpretation of the results were discussed.

*Relative Susceptibility of Different Types.* While the greatest differences in the in vitro susceptibility were exhibited by individual strains, there was some indication of differences among the types, even from the small number of strains tested. The outstanding example is Type XXXIII. The five strains of this type that were tested included the three most resistant strains and one that was relatively resistant. Among the strains isolated before chemotherapy was begun, relative resistance to one or more drugs was exhibited by three of eleven Type I strains (from Cases 5, 7 and 10), by two of six Type III strains (from Cases 21 and 22), by three of six Type V strains (Cases 25, 26 and 27) and possibly by one of the four Type VII strains (Case 34). The strains of Type II, IV and XII, numbering four, two and three, respectively, were all highly susceptible.

*Relative Susceptibility to the Three Drugs Used.* In general, the susceptibility to the three drugs was very similar for each strain. About one-half of the strains tested, however, showed a slightly greater susceptibility to sulfathiazole than to sulfapyridine, as indicated by the lower maximum concentration in which visible growth was noted at 48 hours and also by the lower concentration of drug in the cultures from which the surface plates inoculated after 72 hours yielded no growth. Only one strain (obtained from an abscess in Case 41) was more susceptible to sulfapyridine than to sulfathiazole. The end points in the tests with sulfathiazole and sulfamethylthiazole were the same for two-thirds of the strains tested. The remaining strains were equally divided between those showing a somewhat greater effect from sulfathiazole and those in which the methyl derivative appeared to exert a slightly greater effect. Wide differences were very infrequent.

*Strains Obtained Early in the Disease (Third Day or Earlier) from Uncomplicated Cases of Pneumonia.* If there were any correlation between the susceptibility of strains to any drug and the response of the patient to treatment with that drug, one would expect to detect it in this group. Of the 23 patients in this category, all of whom were treated with either sulfapyridine or sulfathiazole, six had positive blood cultures and four, including one of the latter, were treated with specific serum in addition to chemotherapy.

The serum treated patients are of especial interest. Two of them had Type I pneumonia and failed to show any marked improvement after 24 hours of drug treatment. One of them (Case 5) vomited excessively with sulfathiazole therapy but had an adequate blood concentration at the time serum was given. This was done partly because of the vomiting. The second patient (Case 7) was treated with sulfapyridine and had a high blood level before the serum was given. The pneumococci isolated from both these patients before drug therapy were relatively resistant, the former being the most resistant Type I strain in this group, as judged from the cultures at 72 hours. Two sulfapyridine treated Type II cases (numbers 13 and 16) were given serum because of relapses of the pulmonary infection. One of these patients was the only one of the 23 early cases in this group who died.

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The original strains in both instances were highly susceptible to the drugs. These cases will be considered separately later. Of the remaining 19 patients, 14 had a critical drop in temperature and pulse rate within 36 hours and 5 responded more slowly. There was no correlation between the duration of fever after the drug treatment was begun and the susceptibility of the original strain to the drug used. However, none of the strains isolated from these cases before treatment was highly resistant to the drugs.

*Strains from Patients Treated Late in the Disease and from Those Having Complicating Systemic Disease.* None of the strains isolated from the 11 cases in this group was resistant to the drugs in vitro, although the end points obtained with the various strains exhibited some differences. Furthermore, there was no definite correlation between the degree of susceptibility, as indicated by these end points, and the clinical response of the patients. Three of the 11 patients died in spite of chemotherapy, supplemented in 2 of the cases by serotherapy. One fatal case of Type VII pneumonia (Case 34) will be considered later, since additional cultures obtained during the course of treatment were also tested. In Case 11, treatment with sulfathiazole was begun on what was probably the tenth day of the disease. The patient was extremely ill with Type I pneumococcus pneumonia and bacteremia and died after 36 hours of drug therapy. The third patient who died had a non-bacteremic Type I pneumonia and rheumatic heart disease with some decompensation at the time treatment was begun (Case 12). He showed no response to sulfapyridine therapy, which was carried on for 5 days and was then discontinued only because of the development of gross hematuria. Specific serum was also given without untoward reaction on the second day of the chemotherapy. The concentrations of drug attained in the blood of these three fatal cases were considerably greater than those required to induce marked inhibition of growth of their respective strains in vitro.

One patient of this group (Case 21), in whom treatment with sulfathiazole for a severe pneumonia was started on the fourth day, showed a rather slow improvement. The Type III pneumococci obtained from the sputum of this patient before treatment were less susceptible than the strains from all but one of the other Type III cases studied. This patient had evidence of abscess formation in his lung and he may also have had underlying tuberculosis, although this could not be established definitely.

*Comparison of Susceptibility of Strains Isolated at Different Times from the Same Patient.* Of especial interest are the seven patients in whom strains of the same type were isolated both before treatment and after several days of chemotherapy, since they offered an opportunity to learn whether drug-resistance could be induced in the usual course of treatment. Only three of these patients (numbers 13, 16 and 34) were treated for pneumonia; the other four received the drugs for focal pneumococcal infections. Two had meningitis (Cases 38 and 39), one had lateral sinus thrombosis which was



# SULFATHIAZOLE IN THE TREATMENT OF PNEUMOCOCCUS PNEUMONIA\*

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IN view of the remarkable therapeutic effects obtained with sulfanilamide and sulfapyridine it was to be expected that investigators would direct their efforts to the preparation of derivatives or modifications of these drugs which, while retaining their therapeutic activity, would be free of the undesirable side-effects so commonly encountered in their use. One of the products recently made available is sulfathiazole (2-sulfanilamidethiazole), which was independently synthesized by Fosbinder and Walter,<sup>1</sup> and Lott and Bergeim.<sup>2</sup>

Several reports on the pharmacology and experimental use of this drug in animals and man have recently been published. From these the following observations may be cited. It is more soluble than sulfapyridine<sup>3</sup> and is more rapidly absorbed from the intestine.<sup>3,4,5</sup> Following the administration of a single oral dose in man, the maximum blood level is usually attained in two hours, and is fairly well maintained for from four to six hours.<sup>3</sup> It is more rapidly excreted, and to a greater extent, than sulfapyridine.<sup>3,4,5</sup> The conjugated, or acetylated form occurs in lower proportion in the blood and urine than is the case with sulfapyridine.<sup>4,5</sup>

In pneumococcus infections in mice the therapeutic efficiency of sulfathiazole was found to equal that of sulfapyridine, when administered as 1 per cent of the diet.<sup>4,6</sup> However, when given as a lesser percentage of the diet,<sup>6</sup> or when administered in suspension by mouth,<sup>4,7</sup> sulfapyridine appeared to be the more efficient of the two. It has been suggested by Long that this apparent discrepancy may be due to the more rapid disappearance of sulfathiazole from the blood.<sup>4</sup> In the treatment of pneumococcus pneumonia in man this investigator, on the basis of his preliminary experience, believed sulfathiazole to be about as effective as sulfapyridine. Recently Flippin, Schwartz and Rose, from their experience with comparable series of 100 cases each, concluded that sulfathiazole and sulfapyridine are apparently equally effective in the treatment of pneumococcus pneumonia in man. Their mortality rate in the sulfathiazole series was 7.4 per cent, and in the sulfapyridine series 11.4 per cent.<sup>8</sup>

In experimental studies with mice sulfathiazole proved to be definitely less toxic than sulfapyridine when administered parenterally as a single dose of the sodium salt.<sup>4,5</sup> This relationship was apparent also when repeated

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complicated later by meningitis (Case 22), and the fourth had pneumococcal peritonitis and an abdominal abscess complicating a nephrotic syndrome (Case 41).

The Type XXXIII pneumococci isolated in Case 41 were all highly resistant to each of the three drugs. The strain isolated in this case from the peritoneal fluid aspirated before chemotherapy was begun was the most resistant strain obtained from any of the patients in the course of this study. As far as could be ascertained, this patient had not been treated with sulfonamide drugs on any previous occasion. All the three strains tested were resistant to each of the three drugs used in the tests, the differences being irregular. The pneumococci isolated from the blood on the day after sulfapyridine therapy was begun, however, were much less resistant, according to this test, than the original peritoneal strain, and the organisms obtained from the abdominal abscess at autopsy were intermediate in resistance. The patient died after 16 days of intermittent sulfapyridine therapy, chiefly as a result of nephritis. The peritonitis had apparently cleared completely and the large abscess of the abdominal wall was the only evidence that remained of the original infection.

The first strain isolated before treatment in each of the other six patients was susceptible to each of the three drugs. In three of these patients, the results of tests done on all the organisms isolated indicated no change in this susceptibility. One of these three patients (Case 34) had Type VII pneumonia with bacteremia and an underlying luetic aortic aneurysm. Bacteremia persisted during 5 days of sulfathiazole therapy, high concentrations of the drug being maintained in the blood during most of this time. Serum treatment was then given, but, although all subsequent blood cultures were sterile, the patient died. Autopsy showed an extensive pneumonia in addition to the aneurysm. The other two patients both had Type XII pneumococcal meningitis and succumbed in spite of persistent treatment with sulfapyridine, supplemented at first with serum. All the organisms that were isolated from these two patients and tested showed equally high degrees of susceptibility to the three drugs. In Case 39 the last strain was obtained after 5 days and in Case 38 after 15 days of chemotherapy.\*

In Case 22, treatment with sulfapyridine and serum was given for lateral sinus thrombosis and Type III pneumococcemia prior to operation. The patient improved, blood cultures made after the operation were sterile and the drug therapy was discontinued after a week. Shortly thereafter, fever recurred, sulfapyridine therapy was resumed but, in spite of it, meningitis developed and subsequent blood cultures were again positive. The strain obtained from the blood of this patient before treatment was susceptible to the three drugs used, but, less so than any of the Type III strains obtained from five other patients studied. The strain isolated from the blood 13

\* In a recent fatal case, Type XIX pneumococci obtained from spinal fluid after 24 days of intensive sulfapyridine treatment were only slightly more resistant to sulfapyridine and sulfathiazole than the pneumococci obtained before the treatment was begun.

oral doses were administered to rats and monkeys.<sup>5</sup> When repeated oral doses were administered to mice sulfapyridine appeared to be the less toxic of the two; but when the dose was kept at therapeutic levels no difference in toxicity could be noted.<sup>5</sup> The principal pathologic change in these animals, if any were present, was renal damage.<sup>9</sup> Following the administration of sulfathiazole to white rats precipitation of the drug was found to occur in the distal collecting tubules.<sup>10</sup>

In man during the treatment of pneumonia with sulfathiazole some temporary impairment of renal function has at times been noted, as evidenced by oliguria, low specific gravity and diminished urea clearance.<sup>3</sup> However, a complete return to normal function usually occurred during the continued administration of the drug.<sup>8</sup> Occasionally anuria with azotemia occurred.<sup>11</sup> In one case anuria for 48 hours followed the cessation of therapy.<sup>4</sup> Mild<sup>4</sup> or microscopic<sup>3, 8, 11</sup> hematuria has been noted in several instances. Occasionally gross hematuria has been observed.<sup>11, 12</sup> In one case recently reported the collecting tubules of the kidneys at autopsy were dilated and many were partially or completely obstructed by deposits of crystalline material.<sup>13</sup>

Other toxic effects occasionally observed during the administration of sulfathiazole in man are nausea and vomiting,<sup>3, 4, 8, 11</sup> dizziness,<sup>11</sup> drug fever,<sup>4, 8, 11</sup> drug rashes,<sup>3, 4, 8, 11</sup> and conjunctival and scleral congestion.<sup>4, 8, 11</sup> However, the nausea and vomiting are reported to have been mild and infrequent and not to be compared in intensity and persistence with that so frequently seen attending sulfapyridine therapy.<sup>3, 4, 8, 11</sup> Cyanosis due to the drug has either not been noted<sup>3</sup> or has been minimal.<sup>11</sup> Neither have the more serious blood dyscrasias been reported,<sup>3, 8, 11</sup> although mild leukopenia with granulocytopenia has been observed.<sup>11</sup>

During the past six months a clinical trial of sulfathiazole in the treatment of a series of 50 cases of pneumococcus pneumonia in Pittsburgh has been conducted. All cases included in this series had roentgenographic evidence of consolidation, and either a positive blood culture or sputum in which the pneumococcus was the predominating organism. A history, physical examination, urine analysis, blood count, blood culture, sputum examination, and roentgenogram of the chest were obtained routinely on admission. Blood cultures were taken at two-day intervals or more frequently when indicated. Identification of the type of pneumococcus present in the sputum was made by the Neufeld method. There was no selection of cases for treatment. A tentative diagnosis of pneumonia having been made, sputum and blood were obtained for bacteriological study, and sulfathiazole treatment was instituted at once without waiting for laboratory reports, thus avoiding unnecessary loss of time.

Included in this report are all cases of pneumococcus pneumonia treated with sulfathiazole, with the exception of three which terminated fatally in less than 24 hours after admission, after each had received only 8 grams of the drug. The series included cases of Types I, II, III, IV, V, VI, VII,

days after drug treatment was started was only slightly more resistant to the drugs, as judged by the result of the cultures made after 72 hours, while the organisms grown from the spinal fluid 2 days previously exhibited considerable resistance to the drugs.

The course of events in the two patients with Type II pneumonia, each of whom had a relapse of the pulmonary infection, one during the course of sulfapyridine treatment (Case 16) and the other shortly after treatment with this drug was discontinued (Case 13), is shown in figures 3 and 4, respectively. In the former, the relapse occurred after 5 days of treatment at a time when the patient seemed much improved—temperature, pulse and leukocyte count were normal, and the blood culture which had been positive during the first two days of treatment had become sterile. With the relapse of fever, rusty sputum recurred, the pulmonary lesion extended from the right lower lobe to involve the entire right lung and the blood culture again was positive. Following serum therapy, and without discontinuing the drug, the blood cultures again became sterile, but the patient died four days later. The blood concentrations of the free sulfapyridine at the time of relapse and again before death were 6.3 and 8.1 mg. per cent, respectively. At autopsy the only significant finding other than the acute lobar pneumonia was a small encapsulated empyema. The organisms obtained from the sputum of this patient before treatment were highly susceptible, while those grown from a second sputum at the time of the relapse were highly resistant to sulfapyridine.

Case 16 was that of a non-bacteremic Type II pneumonia who was treated with sulfapyridine on the first day of illness and had what appeared to be a good response within 36 hours (figure 4). The drug treatment was continued for a total of 5 days, the temperature and pulse remaining normal. At the end of this time the patient still appeared well except for slight vomiting, and the leukocyte count was normal. Treatment with the drug was then stopped. A few hours later the temperature, pulse and respirations rose. On the following day the sputum was again rusty and the pneumonia had spread from the right upper to involve the right lower lobe. Further treatment with sulfapyridine resulted in a drop in temperature, but the elevation of pulse rate and the symptoms persisted until after specific serum was given. As in Case 13, so in this case, the pneumococci isolated from the sputum before treatment were highly susceptible, while the Type II organisms grown from a second sputum during the relapse were highly resistant.

In each of the last three cases, the strains isolated after treatment showed greater resistance not only to sulfapyridine, the drug with which the patients were treated, but also to sulfathiazole and to sulfamethylthiazole. Of the later cultures, such differences as were noted in the relative resistance to the three drugs were similar to those exhibited by the original cultures made before the chemotherapy.

VIII, IX, XI, XIII, XV, XX, XXI, XXII, XXIV, and XXV. The patients' ages varied from 20 to 82 years, the average age of those who recovered being 44. The general degree of severity of infection was at least equal to that usually encountered, as shown by the fact that 16 patients, or 32 per cent of the total, had positive blood cultures on admission. Four patients were admitted on the first day of the disease, 9 on the second, 9 on the third, 8 on the fourth, 9 on the fifth, 4 on the sixth, and 2 on the seventh. In five cases the date of onset was uncertain. Sulfathiazole was administered orally in all cases in dosage similar to that employed in sulfapyridine therapy. Four grams were administered at the outset, followed by 1 gram every four hours. In a few cases the interval between doses was reduced to three hours. The total quantity given to each patient varied from 7 to 75 grams, the average being 33 grams. Blood sulfathiazole determinations, urine examinations, and complete blood counts were made daily during the course of treatment.

In this series of 50 patients four deaths occurred—a mortality rate of 8 per cent. Of those who recovered, several had additional physical disabilities. One patient had chronic interstitial pneumonia with calcification of the pleura on the opposite side, another had post-tuberculous fibrosis of the right apex, two had syphilis, one had active thyrotoxicosis with auricular fibrillation, one had advanced arthritis deformans, and two suffered from acute and chronic alcoholism.

Thirty-four patients had negative blood cultures; of these one died. This (case 1) was a 49-year-old woman with Type III pneumonia who was admitted on the sixth day of her illness. Immediately preceding the development of pneumonia she had had a cold of several weeks' duration; and prior to that she had been in poor health for several years, during which time she suffered from shortness of breath, substernal pain on exertion, poor appetite and loss of weight. Two days after admission she developed asthma and pulmonary edema. This was followed by stupor, convulsions, coma, and death on the following day. On the last day of her illness her blood non-protein nitrogen, which had been 33.3 mg. per 100 c.c. on admission, rose to 96 mg., and her blood sulfathiazole to 16 mg. Whether the final train of events was due to the breakdown of an already embarrassed cardio-renal system under the stress of acute infection, or whether it was due in greater or lesser degree to the effect of the drug must remain a matter for conjecture, as permission for autopsy was refused. A rather high blood sulfathiazole level (12.9 mg. per cent) within 12 hours of the onset of treatment suggests that some degree of kidney insufficiency existed at the onset of drug treatment.

Sixteen patients had positive blood cultures; of these three died. One (case 2) was a 74-year-old woman with Type III pneumonia who had been ill for two weeks prior to admission, but in whose case the date of onset of the pneumonia was uncertain. She promptly developed pulmonary edema and died within 36 hours of admission.

the feet at right angles to the legs. A "cradle" avoids such pressure as well as facilitates the use of sandbags or splints to hold the extremities in correct alignment. An electric lamp can be suspended from the frame of the "cradle" to provide warmth or therapy.

The spine is the most important structure from the standpoint of preserving normal relationship, because if the spine becomes fixed in its typically deformed position of flexion and rotation, surgery cannot correct it. The firm bed with one pillow under the head and a small support to maintain lumbar lordosis will go far toward preventing spinal deformities. However, if there is a tendency for the dorsal kyphosis and the flexion of the hips to increase, small supports (such as a folded towel or a small pillow) can be used at the point of maximum kyphosis<sup>9</sup> and under the sacrum. This simple means (demonstrated in figure 7) will soon correct both the kyphosis and the tendency to hip flexion. At first, the supports should be

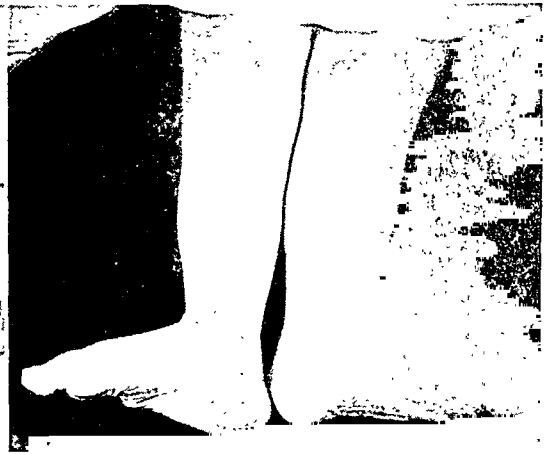
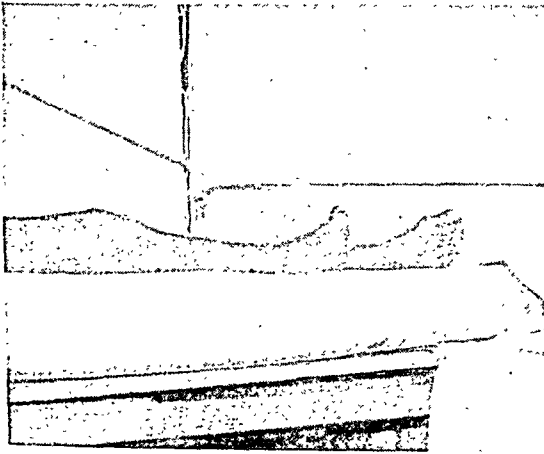


FIG. 5. (*Left*) Usual position of lower extremities when resting.  
FIG. 6. (*Right*) Deformity caused by pressure of bed clothes.



FIG. 7. (*Left*) Effective method of extending hips and back.  
FIG. 8. (*Right*) Posterior dislocation of tibia on femur caused by pillow under thigh.

very thin to avoid undue strain, but they can be gradually increased in thickness. A support as large as the pillows shown in the illustration is rarely needed and should be used only under close supervision. If flexion of the spine is prevented, there is little danger of the development of scoliosis.<sup>24</sup>

The hips should be considered in connection with the spine because deformities in these structures go hand in hand. Distortion in the trunk changes the line of gravity and necessitates flexion of the hips. Similarly, a fixed flexion deformity of the hips causes a forward tilting of the pelvis which in turn precipitates that extreme degree of lumbar lordosis which invariably accompanies flexion of the hips. A pillow placed under the sacrum as noted above is usually sufficient to control the early tendency to hip flexion.

Rotation and adduction deformity of the hips is quite another matter. The lower extremities should be held in a position midway between internal and external rotation, and at frequent intervals the thighs should be separated so as to avoid contraction and shortening of the strong adductor muscles. These positions are maintained by sandbags or, when necessary, by splints. All forces used to prevent deformities in the hips should be exerted above the knees because any force exerted at the foot or leg will first have to act through the ankle and knee joint, thus losing considerable effectiveness and putting strain on the ankle and knee supports. In the acutely inflamed hip, a short period of immobilization in a plaster of Paris spica will do much to prevent threatened deformity.

It can be said without hesitation that the knees are the most important of the large joints to consider from the standpoint of the prevention of deformities. This is true because they are so universally involved and so frequently abused. The most common mistake is to allow the patient to lie with a pillow under his knees in an effort to relieve his pain. This flexion of the knees rapidly causes a fixed contraction of the posterior capsules and the hamstring muscles. The patient who walks on a flexed knee joint precipitates distortion in both lower extremities and throughout the trunk. As a rule, pillows that are used to relieve the pain in the knees are placed under the thighs and not under the legs. The supporting structures of the acute joints are weakened. Hence, the weight of the tibia stretches the muscles and the joint capsule, allowing the tibia to become posteriorly displaced on the femur (figures 8 and 9). The posterior displacement of the tibia causes a deformity which resists correction more than any distortion of the large joints. This whole chain of circumstances can be prevented by complete immobilization of the involved lower extremity in circular plaster of Paris casts until the acute inflammation has subsided, and then a posterior splint or appropriate brace can be used to maintain the correct position.

The ankles and the feet are the next joints to be considered. While patients are in bed, splints are used to maintain the feet and ankles in normal dorsi-flexion and inversion. When the patient becomes ambulatory, the footwear should be such that it maintains the correct alignment of the feet, ankles and knees.

Another (case 3) was a 70-year-old man with Type II pneumonia, first seen on the sixth day of his illness with consolidation of the right upper lobe. On admission his blood sugar, non-protein nitrogen and creatinine were respectively 270, 86, and 3 mg. per 100 c.c. Because of his azotemia, when his temperature fell to normal within 36 hours of the institution of treatment, the dosage of sulfathiazole was sharply reduced. Notwithstanding the favorable temperature curve the patient's condition steadily became more grave. He died four days following admission after having received a total of 17 grams of the drug.

The other (case 4) was an obese 79-year-old man with Type XX pneumonia who was admitted on the fourth day of his illness. He also had diabetes mellitus. This patient's temperature fell to normal within 24 hours of the institution of treatment and a roentgenogram a few days later showed considerable clearing of the pneumonic involvement. However, during his stay in the hospital his pulse rate varied from 120 to 130 with frequent extrasystoles, and the roentgenogram showed a very broad heart shadow. His blood non-protein nitrogen was 54.1 mg. per cent. On his sixth day in the hospital he suddenly developed abdominal distention and vomiting, following which he rapidly sank into coma and died the following day. An electrocardiogram taken a short time before death showed delayed intraventricular conduction. At autopsy relatively little pneumonia was found. The pancreas showed hyalinization of the islets of Langerhans and fatty infiltration. The kidney showed combined lesions of arterial nephrosclerosis and nephrolithiasis. Analysis of the granular stones present in the pelvis showed them to contain 0.1 per cent sulfathiazole, from which it was concluded that the sulfathiazole was absorbed by the small granular stones already present. The liver cells showed fatty infiltration and toxic swelling which may have resulted from the effect of the drug on a liver already damaged by diabetes and passive congestion. The heart showed interstitial myocarditis.

Table 1 shows the mortality statistics analyzed from the standpoint of type of infection and presence of bacteremia. Table 2 shows these statistics analyzed from the standpoint of age.

In 29 patients (58 per cent of the total number), including eight patients with bacteremia, the course of the disease appeared to have been prematurely terminated by the administration of sulfathiazole, recovery from the acute phase, as evidenced by subsidence of fever, reduction of pulse and respiratory rates and a marked improvement in the subjective symptoms, having occurred in from 10 to 60, or an average of 25 hours after treatment was instituted. Several other patients in the series also recovered rapidly, but in their cases this feature lacked significance, as either their illness was already far advanced when treatment was started, or the date of onset of their infection was unknown.

In a few cases a low-grade irregular fever, unattended by other symptoms or signs of illness, followed apparent recovery from the active pneumonic



disease, the temperature falling by crisis on the twelfth day of the illness, and the patient recovered.

*Discussion:* We are unable to offer any satisfactory explanation as to the refractoriness to the sulfapyridine in this case. In this series no study was made of the rate and frequency of development of antibodies, which, however, it is our intention to follow in future cases. There exists some possibility that delayed or absent development of antibodies in occasional cases may prove to be the cause of an apparent failure of effect of sulfapyridine.

*Case 2.* This 34 year old female had a Type XVIII pneumococcus in her sputum and a negative blood culture. She was given 27 grams of sulfapyridine over a period of seven days beginning on the third day of the illness. The roentgen-ray showed a consolidation of the left lower lobe. The leukocyte response was from 14,300 to 20,600. The patient continued to run a low-grade spiking fever from 100° F. to 103° F. for 12 days after the sulfapyridine was discontinued.

*Discussion:* The consensus of clinical opinion was that this patient probably had had a virus type of pneumonia with an incidental pneumococcus in the sputum. In any event, there was a complete absence of therapeutic response to the sulfapyridine.

*Case 3.* This patient was a 65 year old female who had had recurrent attacks of bronchitis for years and previous admissions for bronchopneumonia. The sputum contained a Type VIII pneumococcus. A blood culture was not taken. The patient had had a low-grade spiking fever for two weeks before sulfapyridine was instituted. Sulfapyridine had no beneficial effect and had to be withdrawn after only 10 grams had been administered, because of severe nausea and vomiting. The pneumonia eventually cleared after a slow course and the patient was discharged, only to return two weeks later with a recurrence and again with a Type VIII pneumococcus in the sputum. Sulfapyridine again produced severe nausea and vomiting and had to be discontinued. The patient eventually recovered spontaneously.

*Discussion:* The most definite cause for the apparent failure of the sulfapyridine in this case consists of the probable presence of considerable previous lung damage for the existence of which we have good evidence in the recurrent nature of the attacks. In addition it should be noted that on two occasions the drug had to be discontinued before an adequate dose was given because of the severe nausea and vomiting.

*Case 4.* This 51 year old male had a Type VIII pneumococcus in the sputum, blood, and empyema fluid. The roentgen-ray showed a spread from the right lower lobe to the left lower lobe and the blood culture continued positive after a total of 20 grams of the drug had been given. The leukocyte count fell from 22,100 to 12,400. The patient was then given rabbit serum and within three days the blood was sterile and convalescence uneventful. The empyema did not require surgical drainage.

*Discussion:* No adequate explanation for the absence of response in this case can be given at this time, and it may well represent a true failure for the effect of the drug. Again in this case the possibility exists that there was a delayed or absent development of antibodies by the patient. However, the therapeutic use of the antibodies present in the rabbit serum was sufficient

TABLE I

Mortality Statistics. Analysis as to Type and Presence of Bacteremia.

Type	All Cases		Non-bacteremic Cases		Bacteremic Cases	
	Number	Deaths	Number	Deaths	Number	Deaths
I	10		8		2	
II	5	1	2		3	1
III	8	2	6	1	2	1
IV	3		2		1	
V	2		1		1	
VI	1		1			
VII	6		4		2	
VIII	4		2		2	
IX	3		2		1	
XI	1		1			
XIII	1				1	
XV	1		1			
XX	1	1			1	1
XXI	1		1			
XXII	1		1			
XXIV	1		1			
XXV	1		1			
Total	50	4 (8%)	34	1 (2.9%)	16	3 (18.8%)

TABLE II

Mortality Statistics. Analysis as to Age.

Age	20-29	30-39	40-49	50-59	60-69	70-79	82	Total
Cases	11	7	12	10	4	5	1	50
Deaths			1			3		4

process and continued for several days after sulfathiazole administration had been discontinued. A similar fever has also been noted in cases treated with serum<sup>14</sup> and with sulfapyridine. While its mechanism is obscure it is apparently without important significance. Regardless of the immediate effect of sulfathiazole treatment on the temperature curve, almost all patients experienced a marked amelioration of symptoms. They appeared much more relaxed and comfortable, lost their anxious expression, and usually rapidly regained their appetite.

Leaving out of consideration two cases with evidence of impairment of renal function, the concentration of sulfathiazole in the blood varied from 2.0 to 12.8 mg. per 100 c.c., averaging 6.2 mg. No direct relation could be seen between the blood level and the clinical response. Four patients with blood levels below 3 mg. per cent recovered promptly and prematurely by crisis, while one patient with blood levels constantly above 5 mg. per cent had a protracted course. From this standpoint also a marked resemblance is shown to cases treated with sulfapyridine. The leukocyte count in general

to swing the balance in favor of the patient. It may well be that future studies of antibody formation in sulfapyridine-treated pneumonias may therapeutically be of benefit as an indication of the type of case in which the addition of rabbit serum to the use of sulfapyridine would be of value.

*Case 5.* This male child of two years was given a total of 25.5 grams of sulfapyridine beginning on the fourth day of his illness. The leukocytes rose from 16,200 to 24,800, while the hemoglobin fell from 63 per cent to 49 per cent. No pneumococcus could be obtained from nasal or throat cultures, but a roentgen-ray showed a consolidation at the left base. A blood culture was not done. There was a transient microscopic hematuria which cleared during continuance of the drug. There was a prompt drop in temperature after a total of eight grams of sulfapyridine was given, followed by a rise the following morning, coincident with a spread from the left lower lobe to the left upper lobe. The temperature then fell by lysis after three days, and the patient recovered.

*Discussion:* A possible explanation for the failure of the drug in this case is that the pneumonia may have been due to some organism which is unaffected by sulfapyridine.

*Case 6.* This was a 32 year old nurse whose sputum did not contain a pneumococcus and who was admitted on the third day of her illness. The roentgen-ray showed a left lower lobe consolidation. After 7 grams of sulfapyridine were given in 24 hours with a drop in temperature from 104.0° F. to 100.0° F., the drug had to be withdrawn because of nausea and vomiting. There was a rise to 103.6° F. two days later, and the drug was recommenced with only a gradual response over a period of three days. The patient recovered.

*Discussion:* Two possible factors are present to account for the apparent failure of the drug in this case. The first is the absence of any specific type of organism in the sputum, and the second is the inadequate dosage resulting from the necessity of discontinuing the sulfapyridine because of the nausea and vomiting.

*Case 7.* This patient was a two and a half year old girl admitted on the fourth day of her illness. The sputum contained a Type XIV pneumococcus. A blood culture was not taken. The roentgen-ray showed a right lower lobe consolidation as well as a pleural effusion. The patient was given a total of 25 grams over a period of 12½ days, but continued to run a low-grade fever for 15 days. The hemoglobin fell from 54 per cent to 35 per cent, and two small transfusions were given on the thirteenth and fourteenth days. Two thoracenteses revealed thin purulent fluid which eventually cleared without surgical intervention.

*Discussion:* A good cause for the apparent failure of effect of the sulfapyridine in this case is unquestionably the presence of the empyema.

#### COMPLICATIONS OF SULFAPYRIDINE THERAPY

Complications of this form of therapy were of the usual types associated with the use of this group of drugs. The following table lists the frequency of complications in this series.

followed the course of the disease, falling with clinical evidence of recovery. However, in six cases a definite stimulating effect of the drug on leukocytosis is suggested by the fact that the count remained elevated after all fever had subsided as long as administration of the drug was continued.

Toxic effects of sulfathiazole administration were inconspicuous. Observations on this phase of the study have been gathered from a series of 65 patients, since 15 cases of non-pneumococcic pneumonia were also treated by this method. Five patients had been nauseated and two patients had vomited before drug treatment was started; in their cases these symptoms promptly subsided during treatment. After sulfathiazole treatment had been instituted nausea occurred in eight, vomiting in six, and diarrhea in two cases of this group of 65. Except in the case of one patient, who was nauseated over a period of three days but who did not vomit, all three symptoms were isolated occurrences and of mild degree, and never made it necessary to interrupt the continuity of treatment. From our experience thus far this comparative absence of undesirable gastrointestinal symptoms appears to be the most striking feature of the clinical picture of patients on sulfathiazole treatment as contrasted with that of patients treated with sulfapyridine.

Microscopic red blood cells were found on occasion in the urine of 24 patients to whom sulfathiazole was administered. In seven cases they were present on admission. No instances of gross hematuria were encountered. In this connection it is interesting to note that sulfathiazole crystals were reported as present in one or more specimens of urine from 36 of the 65 patients receiving this drug, although no cases of sulfathiazole calculi were encountered.

In addition to the case (case 1) already cited one other patient was observed presenting evidence of renal impairment with azotemia possibly directly due to the administration of sulfathiazole. This (case 5) was a 77-year-old woman with Type I pneumonia, who was admitted on the fourth day of her illness with consolidation of two lobes. On admission her urine contained a trace of albumin, an occasional hyaline cast, and a few red blood cells. Her fever subsided by crisis within 12 hours of the institution of sulfathiazole treatment. Blood taken 36 hours after admission (24 hours after recovery from pneumonia) contained 66.6 mg. non-protein nitrogen and 13.2 mg. sulfathiazole per 100 c.c. Three days later the blood non-protein nitrogen had risen to 75 mg. and the blood sulfathiazole to 20 mg. Mild delirium and a slight secondary rise of temperature developed. Following cessation of sulfathiazole therapy and free administration of fluids parenterally, rapid improvement occurred. Within three days the blood non-protein nitrogen had fallen to 48.8 mg., and a few days later to 34.7 mg. The patient made a complete recovery. Even though the functional capacity of this patient's kidneys may have been impaired before treatment, as suggested by her age and the laboratory findings on admission, and perhaps further adversely affected by the infectious process, one cannot ignore the possible direct relationship between the administration of the drug and the

TABLE III  
Complications of Sulfapyridine Therapy

Complication	No. of Cases	Percentage
Rash .....	1	0.8%
Nausea .....	83	68.0%
Vomiting .....	72	59.0%
Drop in hemoglobin .....	20	16.3%
"    "    "    —due to drug .....	8	6.3%
"    "    "    —possibly due to other causes...	12	10.0%
Agranulocytosis .....	0	0
Microscopic hematuria .....	12	10.0%
Gross hematuria .....	5	4.1%

In this study we were not impressed by the production of cyanosis by the drug, nor did we feel that in any case such cyanosis as existed could be attributable directly to its use. An erythematous rash was observed on only one occasion. This disappeared promptly upon discontinuing the drug.

The most constant and annoying complications were those of nausea and vomiting. Nausea of moderate degree occurred in 51 cases, was severe in 32 cases, and appeared to some degree in a total of 68 per cent of the cases studied. Vomiting appeared in 59 per cent of the patients, being moderate or mild in 49 cases and severe in 23 cases. The medication was discontinued in 19 cases because of the vomiting. Various measures to combat nausea and vomiting, including sedation, various vehicles for the drug, etc., were used with little effect. As has been repeatedly shown elsewhere, the vomiting is probably central in origin.

As has been shown by Long<sup>3</sup> and others, sulfapyridine probably has much less frequently produced anemia or agranulocytosis than has sulfanilamide. In 102 of the 122 cases there was little or no change in the hemoglobin. In 12 of the remaining 20 cases the drop in hemoglobin could well have been caused by some complication of the infection, such as the development of an empyema or a bacteremia, or by some other factor such as replacement of body fluids following initial dehydration with blood concentration before hospitalization. Eight of the cases showed a drop in hemoglobin which was probably definitely related to the use of sulfapyridine. In none of these was the anemia alarming, and in all of these the hemoglobin resumed normal levels within a satisfactory period of time after the individual had recovered from the illness. In no case was the anemia severe enough to warrant cessation of the therapy. Jaundice did not appear as a complication of the drug therapy.

Repeated leukocyte counts were done in 112 cases. Of these, 47 showed a strikingly good leukocyte reaction during sulfapyridine therapy, while 65 showed no leukocytosis or a diminution in circulating leukocytes. No cases developed an agranulocytosis, and in no case did the leukocyte count fall below 4,500. Of the four deaths directly due to the pneumonia two had a leukocyte response, and two did not. Of the four deaths due to later complications or to inadequate dosage, all had a good leukocytosis after receiving sulfapyridine.

development of azotemia. This is all the more true because of the well known occurrence of similar complications occasionally attending the administration of sulfapyridine, and because of the experimental and clinical observations previously cited<sup>11, 12</sup> of the precipitation of sulfathiazole crystals in the collecting tubules of the kidneys. In this connection the advisability of liberal administration of fluids during sulfathiazole therapy with the purpose of preventing precipitation or, if this has already occurred, redissolving the precipitate should be stressed.

One other patient with marked azotemia on admission was observed in addition to the fatal case (case 3) already discussed. This (case 6) was a 52-year-old man with Type VI pneumonia involving the right upper lobe. His blood non-protein nitrogen within a few hours of admission was 101.8 mg. per 100 c.c. On sulfathiazole medication he made a prompt recovery from his infection; and the drug was discontinued after 48 hours, during which 15 grams were administered. On the following day his non-protein nitrogen had fallen to 76 mg. and it continued to fall thereafter to normal. He left the hospital apparently completely recovered from his illness.

A rash probably due to sulfathiazole occurred in two cases—in one morbilliform, and in the other purpuric in character. In both cases it appeared after several days of treatment and did not seem to be associated with any increased toxicity or other unfavorable development. However, upon its appearance the drug was promptly discontinued. Both cases recovered. Two patients who exhibited renal impairment developed mild delirium. A third patient was delirious on the second and third days in the hospital, but this could not be ascribed to the medication as it subsided during the continued administration of the drug. Three patients developed a secondary rise of temperature unaccompanied by other symptoms a few days after apparent recovery from the infection, and while sulfathiazole was still being administered. As in each case it subsided promptly upon discontinuing treatment, these may be considered instances of drug fever. Cyanosis when present did not appear to have any relationship to the medication. No instances of serious blood dyscrasias were encountered.

#### SUMMARY

1. The experimental basis underlying the clinical use of sulfathiazole is briefly reviewed.
2. A report is made on the use of sulfathiazole in the treatment of 50 cases of pneumococcus pneumonia in Pittsburgh. Four deaths occurred in this series—a mortality rate of 8 per cent.
3. The general effect on the temperature curve and clinical course of the disease was similar to that observed with sulfapyridine therapy.
4. Nausea and vomiting were rarely encountered, and when present were mild and of short duration.

As regards the effect of sulfapyridine upon kidney function, we were not impressed by the urinary albumin content in any of the cases. Five (4 per cent) of the cases developed gross hematuria and 12 (10 per cent) microscopic hematuria. The latter occasionally might have been a direct result of the disease, but the percentage seems rather high for this cause alone. The development of the gross hematuria in the five cases was acute in onset, and the hematuria cleared rapidly within a few days after the drug was discontinued. Three of these cases were cystoscoped later, and retrograde pyelographic studies failed to show any abnormalities. In addition to these five cases, gross hematuria occurred in a patient with a coronary thrombosis who had had a pulmonary infarct which was mistaken for a pneumonic consolidation, and who consequently was treated with sulfapyridine. She later died a cardiac death, and at autopsy numerous fine needle-shaped crystals were found in the pelvis of both kidneys and plugging both ureteral orifices. At the time, unfortunately, facilities were not available to determine the nature of these crystals.

### DISCUSSION

Study of a series of 122 cases of lobar pneumonia treated with sulfapyridine during the winter of 1938-39 has led us to believe that the drug is unusually effective in this disease. The mortality rate for this series was 6.5 per cent. In the small group of 11 patients with a bacteremia the mortality was only 18.1 per cent. The average dosage per patient was 17.5 grams, given over an average total of four and a half days. There was a good clinical response to the drug, on the average, within 24 hours.

The most constant and bothersome complications of this mode of therapy were nausea and vomiting, nausea being present in 68 per cent of the cases and vomiting in 59 per cent. It is at present our opinion that in many of the 19 cases in which the drug was discontinued because of nausea or vomiting this was unnecessary, and that the patient should be deprived of this valuable therapeutic agent only when the vomiting is unusually severe and intractable. It was our impression, especially with the earlier cases where the drug had been discontinued because of nausea or vomiting after only about 10 grams had been given, that the temperature shortly rose again to former levels requiring additional therapy. We then found that if the drug was resumed, the nausea and vomiting were frequently much less troublesome than previously in the same patient. For these two reasons, therefore, our present routine is to omit the drug if necessary for one or two doses only, the vomiting often having entirely ceased upon resumption of the drug. If the nausea or vomiting should then reappear, which happens much less frequently, it is almost always much less severe than previously.

The production of an anemia following or during sulfapyridine administration is rare and unless unusually severe, is not a contraindication to the continued use of the drug. Although none of these cases developed an

5. Azotemia apparently related to the administration of sulfathiazole was observed in two instances. The importance of adequate fluid administration in its prevention and correction is stressed.

6. No other serious toxic effects were observed.

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agranulocytosis, repeated blood counts should be done at least every two days, and the appearance of a marked leukopenia of course would contraindicate further use of the drug at this time.

The appearance of hematuria is unusually frequent, whether microscopic or macroscopic. Microscopic hematuria is probably no contraindication to further use of the drug, but upon the appearance of gross hematuria it should at once be discontinued. It has been stated recently<sup>3</sup> that sulfapyridine crystals are only present in acid solution, being soluble in alkaline solutions. Following the suggestion of Long and Wood, we have recently begun the use of sodium bicarbonate with each dose of the sulfapyridine, using gram for gram.

In 10 per cent of the patients reported in this series, the sulfapyridine apparently did not influence the course of the disease. It may or may not have been a factor in their recovery. Brief abstracts of these individual cases have been presented. In many of these cases complicating factors existed which probably exerted an adverse influence upon the usual effectiveness of the drug.

#### SUMMARY

1. A review of 122 cases of pneumonia treated with sulfapyridine from November 15, 1938 to April 15, 1939 has been presented.

2. In this series there were eight deaths, representing a mortality of 6.5 per cent.

3. The types of pneumococci found are listed.

4. Brief abstracts of the patients who died have been presented.

5. Brief abstracts of the cases failing to show a good clinical response to this form of chemotherapy have been presented.

6. The complications of sulfapyridine therapy have been discussed.

The authors wish to thank the Directors of Medical Division B, of Surgery, and of Pediatrics for their kindness in allowing us to include in this study certain cases treated on their respective services.

The sulfapyridine used in this study was obtained through the courtesy of Merck & Co.

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# SULFAPYRIDINE THERAPY IN PNEUMONIA: A DISCUSSION OF APPARENT FAILURES AND COMPLICATIONS\*

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## INTRODUCTION

A review of a series of 122 ward and private cases of pneumonia treated with sulfapyridine at St. Luke's Hospital from November 15, 1938 to April 15, 1939 revealed that there were eight deaths in the series, or a mortality of 6.5 per cent. In addition to these eight cases, it was noted that there were seven patients who, although they survived their pneumonia, failed to show a good clinical response to this form of chemotherapy. Believing that a detailed summary of these 15 cases would be of interest at this time, we are presenting the following summaries, after a short preliminary résumé of our statistical findings for the series as a whole.

## AGES

The ages of these patients ranged from two months to 83 years. The distribution of cases is analyzed in table 1. It is noteworthy that in this particular series 49 per cent of the cases were over 40 years of age, and that five of the eight deaths occurred in these older groups.

TABLE I  
Analysis of Ages and Mortality

Ages	No. of Cases	Deaths
0-1 .....	5	0
1-5 .....	11	0
5-10 .....	7	0
10-20 .....	5	0
20-30 .....	15	2
30-40 .....	19	1
40-50 .....	20	1
50-60 .....	22	1
60-70 .....	13	2
70-80 .....	4	0
80-90 .....	1	1

## TYPES OF PNEUMOCOCCI FOUND

The sputum of 87 patients yielded pneumococci either directly by the Quellung method or after passage through mice. The distribution of the cases as to the type of pneumococcus responsible for the pneumonia can be

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# THE PROBLEM OF PNEUMONIA WITH REFERENCE TO CHEMO- AND SERO-THERAPY \*

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IN 1939 Long and Wood <sup>1</sup> reported that the case fatality rate in pneumococcal pneumonia at The Johns Hopkins Hospital had been reduced to 7.2 per cent during the previous year by the therapeutic use of antipneumococcal serum, sulfapyridine, or a combination of these two agents. During the past year we have continued our observations upon the value of chemotherapeutic agents in the treatment of pneumococcal pneumonia in adult patients. Originally, we planned only to continue the use of sulfapyridine, but late in 1939, as a result of the work of McKee et al.<sup>2, 3</sup> and of work carried out in our own laboratory,<sup>4</sup> we decided to give sulfathiazole a clinical trial in the treatment of pneumococcal pneumonia.

Pneumonia was quite prevalent in Baltimore during the winter of 1939-40, with the peak of the disease being reached during the epidemic of respiratory tract infections (influenza?) which occurred in February and early March. It is to be noted in table 1 that in the period from June 20,

TABLE I

The Course of Pneumococcal Pneumonia in Adult Patients in the Johns Hopkins Hospital from July 1, 1935 to July 1, 1940

Year	No. Cases	Bacteremic Incidence		No. Cases Treated							Incidence of Complications	Incidence of Concurrent Disease	Drug Toxic Reactions	Case Fatality Rate
		Admission	Late	Serum	Serum S.P.	Serum S.T.	Serum S.P. S.T.	S.P.	S.T.	S.P. S.T.				
1935-1936	157	21 or 13.3% 23 or 14.5%	2 or 1.2% 14.5%	31 or 19.7%							33 or 21%	31 or 19.7%		30 or 19.1%
1936-1937	181	28 or 15.5% 35 or 19.3%	7 or 3.8% 19.3%	46 or 25.4%							27 or 14.8%	64 or 35.3%		38 or 21%
1937-1938	148	20 or 13.5% 24 or 16.5%	4 or 3% 16.5%	61 or 40.1%							20 or 13.5%	62 or 40.2%		26 or 17.6%
1938-1939	139	23 or 16.5%		31 or 22.3%	8 or 5.7%			100 or 72%			18 or 13.7%	51 or 36.6%		10 or 7.2%
1939-1940	190	25 or 13.2%		1 or 0.5%	25 or 13.2%	12 or 6.3%	5 or 2.6%	68 or 35.7%	66 or 34.7%	13 or 7.0%	15 or 7.9%	69 or 36.3%	38 or 20.0%	15 or 7.9%

S.P. = Sulfapyridine.

S.T. = Sulfathiazole.

\* Received for publication August 10, 1940.

From the Medical Clinic of the Johns Hopkins Hospital and the Department of Medicine of the Johns Hopkins University, Baltimore, Md.

seen by reference to table 2. The most common pneumococcus was Type VIII which was found in the sputum of 13 patients. Other pneumococci found, in order of their frequency, were Types I, III, VI, XIV, V, and XIX. The remaining types listed appeared in one or two cases each. The sputum of 23 cases did not contain pneumococci, and in 12 cases no sputum could be obtained for examination. However, roentgen-rays were taken in all but one case and all showed definite consolidation.

TABLE II  
Analysis of Sputum Typing, Bacteremia, and Mortality

Pneumococcus Types	No. Cases	Blood Cultures		Deaths
		Taken In	Positive In	
I	11	10	7	1
II	1	1	0	0
III	10	7	1	3
IV	2	0	0	0
V	7	7	1	0
VI	8	4	1	0
VII	1	1	0	0
VIII	13	7	1	1
IX	1	0	0	0
X	2	1	0	0
XIII	1	0	0	0
XIV	8	1	0	0
XV	1	1	0	0
XVII	1	1	0	0
XVIII	2	2	0	1
XIX	5	2	0	0
XXI	1	1	0	0
XXII	2	0	0	1
XXIII	1	0	0	0
XXIV	1	0	0	0
XXV	1	1	0	0
XXVII	1	1	0	0
XXIX	1	1	0	0
XXXI	1	0	0	0
XXXII	1	1	0	0
XVI and XXIX	1	1	0	1
I and III	1	1	0	0
VI and XIV	1	1	0	0
Untyped	35	19	0	0
TOTALS	122	72	11	8

#### BACTEREMIA

Blood cultures were taken in 72 cases. Of these, 11 were positive, seven cultures yielding a Type I pneumococcus, and one each Types III, V, VI, and VIII. One patient with a Type I bacteremia and one patient with a Type III bacteremia died. The other nine cases of bacteremia survived. Of the remaining six deaths, in two cases blood cultures were not taken, and four were sterile on one occasion at least.

1939 to July 1, 1940, a total of 190 adult patients ill with pneumococcal pneumonia were treated in the wards of The Johns Hopkins Hospital. This represents the greatest number of admissions for this disease in the last five years.

In determining the effect of therapeutic agents which are used in the treatment of pneumonia, certain factors must be taken into consideration. The age of the patient always has a definite bearing upon the course and severity of pneumococcal pneumonia, it being well known that the prognosis in this disease becomes less favorable as the age of the adult patient increases. Hence, it is of importance in evaluating our results during the past year to make certain that there has not been a significant shift in the age group distribution of the treated patients. Table 2 shows that there has not been a

TABLE II

Age Incidence of Adult Patients Ill with Pneumococcal Pneumonia in the Johns Hopkins Hospital from July 1, 1935 to June 20, 1940

Year	15-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	80-89 years
1935-36	9.3%	29.7%	28.2%	15.4%	10.3%	3.8%	2.6%	0.7%
1936-37	8.4%	24.3%	26.0%	16.4%	11.9%	7.9%	4.0%	1.1%
1937-38	14.2%	22.9%	17.2%	22.0%	11.9%	8.6%	2.4%	0.8%
1938-39	5.1%	22.0%	28.8%	20.3%	8.5%	11.0%	4.3%	0.0%
1939-40	7.4%	25.8%	28.3%	16.8%	12.4%	7.8%	1.5%	0.0%

significant change in the age distribution of our pneumonia patients during the past year. Another factor which is of considerable importance in assessing the value of therapeutic procedures in the treatment of pneumonia is whether or not the patient ill with pneumonia is suffering from a concurrent disease which is known to have an unfavorable influence on the course of pneumonia. Among such conditions are rheumatic heart disease, hypertension with heart disease, arteriosclerotic heart disease, diabetes, chronic alcoholism, pregnancy, asthma, and certain operative procedures. A review of our 190 patients ill with pneumococcal pneumonia showed that 36.3 per cent of them were suffering from one or more major concurrent diseases. This incidence did not vary markedly from that reported during the previous four years.

A third factor of great importance in determining the severity of pneumonia is whether or not bacteremia is present when treatment is begun. It is established that the presence of bacteremia makes the prognosis of pneumonia very poor. As is shown in table 3, during the past five years, 30 out of 38 untreated patients ill with pneumonia and in whom the presence of bacteremia had been determined, succumbed to the disease. During the past year 13.2 per cent of the patients had a pneumococcal bacteremia at the time they entered the hospital. This bacteremic incidence is somewhat, but not significantly, lower than that of last year. Again, as is to be noted in table 1,

## ROUTINE OF ADMINISTRATION OF SULFAPYRIDINE

Sulfapyridine therapy was begun on the average on the third day of the illness. An average of 17.46 grams per patient was given for an average of 4.55 days. The temperature fell to 100° F., on the average, within 19.03 hours. Sulfapyridine was given only when a pneumococcus was obtained from the sputum, or if this was not possible, if a roentgen-ray plate showed definite evidence of consolidation. The first dose was two grams of sulfapyridine given by mouth, and one gram was given every four hours thereafter day and night until the temperature remained within normal limits for at least 36 to 48 hours. Routine urinalyses and complete blood counts were done daily until the drug was stopped. Other routine supportive measures for the treatment of pneumonia were carefully carried out.

## DEATHS

In this series there were eight deaths. Brief summaries of these cases follow.

*Case 1.* This was a 26 year old male with severe rheumatic heart disease. The sputum contained Types XVI and XXIX pneumococci. The blood culture was negative. Roentgen-rays showed a right lower lobe consolidation. He was given a total of six grams of sulfapyridine beginning on the first day of the illness. After the drug was begun the leukocytes rose from 12,900 to 22,800. Sulfapyridine was discontinued after only 6 grams because of moderate nausea. He died three days later without further drug therapy.

*Discussion:* This failure of response can be explained by inadequate dosage. This was one of the first cases to be given this drug in this hospital, and the appearance of progressive nausea was felt to be a symptom of toxicity sufficient to cause us to discontinue the drug in this case.

*Case 2.* This was a 37 year old negro with a long alcoholic history. The sputum and blood contained a Type III pneumococcus. The roentgen-rays showed a consolidation involving two-thirds of the right lung. The patient showed an initial good response to the drug, with a drop in the temperature from 104.0° F. to 100.4° F. in 48 hours, and with a rise in leukocytes from 9,000 to 37,800. The following day he showed signs of a spread to the left lower lobe, and died two days later without further response to continued sulfapyridine administration. The patient was acutely delirious throughout his illness and required large doses of paraldehyde. Autopsy revealed an extensive pneumonic consolidation involving the entire left lung and all of the right lung except for small areas at the periphery. There were no other pathological findings. Both kidneys, ureters, and the bladder were normal.

*Discussion:* The alcoholic history and the presence of a Type III pneumococcus bacteremia in combination offer sufficient cause for a failure of response to sulfapyridine in this case. It must be noted, however, that there was an initial good response, and no satisfactory explanation for the spread of the process other than the factors mentioned can be offered at this time.

TABLE III

The Case Fatality Rates in Untreated and Treated Adult Patients Ill with Bacteremic Pneumococcal Pneumonia in the Johns Hopkins Hospital from July 1, 1935 to July 1, 1940

Type	Untreated	Deaths	Serum	Deaths	Serum S.P.*	Deaths	Serum S.T.*	Deaths	Serum S.P. S.T.	Deaths	S.P.	Deaths	S.T.	Deaths
1	1	1	29	10	5	1	3				6		1	
2	1	1	3	2							2			
3	8	8	3	2					1	1	1	1		
4					1	1					1	1		
5	3	2	1	1	1	1					1			
7	1		7	2	1	1	1		1					
8	4	3	4	1	1						3		1	
10	4	3												
12			1										1	
13											1	1		
14			2	1	1	1								
15											1			
16											1			
18													1	
19											1	1		
20	1													
25	1	1												
Untyped	14	11											1	
Mixed											1	1		
3 & 8														
Total	38	30 80%	50	19 38%	10	5 50%	4	0 0%	2	1 50%	19	5 26.3%	5	0

\* S.P. = Sulfapyridine.

\* S.T. = Sulfathiazole.

another year has passed (thus making it two years in all) without a patient ill with pneumococcal pneumonia developing bacteremia after specific therapy had been inaugurated.

A final factor which enters into a consideration of the severity of pneumonia is that of the incidence of complications either present in the patients on entry or developing during hospitalization. It should be noted that three patients had empyema on entry to the hospital and two developed empyema after specific therapy had been instituted. All of the empyemas were caused by type I pneumococci. Ten of the 190 patients developed sterile pleural effusions while in the hospital. Thus, the incidence of complications of the disease, as will be noted in table 1, is the lowest in the last five years.

Hence, we may say that inasmuch as the age distribution of the patients, the incidence of major concurrent diseases, and the incidence of bacteremia on admission were essentially the same as in the previous five years, pneumococcal pneumonia as observed in this clinic in the winter of 1939-40 was probably as severe as it had been in any year during the last five years. It is interesting in view of these findings that the incidence of the complications of pneumonia which developed while the patients were under treatment was very definitely lower during the past year. This decrease probably represents the effect of specific therapy.

*Case 3.* This patient was a 42 year old white male with a strong alcoholic history. The sputum contained a Type III pneumococcus. The blood culture was negative. The roentgen-ray showed right middle lobe and right upper lobe consolidation. The patient was given a total of 7 grams of sulfapyridine beginning on the fourth day of the illness, and the leukocytes rose from 4,000 to 14,000. He was wildly irrational, requiring paraldehyde and restraint. He died 28 hours after admission without response to the drug.

*Discussion:* The same grave predisposing factors which existed in Case 2, i.e., the alcoholic history and the pneumococcus Type III, were present in this case also. In addition, the patient entered the hospital late in the course of the disease, on the fourth day, and received only a total of 7 grams of the sulfapyridine before death.

*Case 4.* This was a 63 year old male with hypertensive cardiovascular disease who had been chronically decompensated for four months prior to admission. The sputum contained a Type XXII pneumococcus. A blood culture was not taken. The roentgen-ray film showed a consolidation of the right lower lobe and of the left lower lobe. It was impossible to date the onset of the pneumonia from the history. The patient was given a total of 18 grams of sulfapyridine for four days before death without any clinical response. The leukocyte count fell from 17,000 to 8,800.

*Discussion:* The patient's age, the existence of decompensation for a considerable period prior to the onset of the pneumonia, the hypertension, and the absence of a leukocyte response were the probable factors in the failure of response to the sulfapyridine in this case.

*Case 5.* This patient was a 66 year old female with a Type I pneumococcus in the blood and sputum. She was given a total of 29 grams beginning on the second day of the illness. There was a good initial response with a drop in temperature from 104.6° F. to 99.4° F. after 8 grams. Then there developed a gradual rise in temperature for four days before death, with a spread from the left lower lobe to all other lobes except the right upper lobe. The patient was given 200,000 units of rabbit serum on the fifth day of the illness without further effect. During this time the leukocyte count fell from 16,200 to 4,900.

*Discussion:* The patient's age and the poor leukocytic response are possibly contributing factors to the absence of a good therapeutic effect of the sulfapyridine. As recently shown by Löfström<sup>1</sup> and Wood and Long,<sup>2</sup> the development of antibodies occurs at about the same time in sulfapyridine-treated cases of pneumonia as in untreated cases, and it is quite possible that in this case, despite the use of artificial antibodies in the rabbit serum, the surplus of toxic antigen was in the end too great for the patient to overcome.

*Case 6.* This was an 82 year old male who was given a total of 21 grams of sulfapyridine for a total of four days beginning on the fifth day of his illness. The sputum contained a Type XVIII pneumococcus. The blood culture was negative. There was a good leukocyte response from 6,100 to 15,600. The temperature fell to normal limits within 72 hours after the drug was begun. Ten days later the patient was gradually allowed up, but during the third week began to run a low-grade spiking fever. At the same time the hemoglobin gradually fell from 80 per cent on admission to a low of 34 per cent. One month after admission an empyema was demonstrated



In planning our procedures for treatment of adult pneumococcal pneumonia patients during the past year, we decided that, with the exception of the pneumonias in which pneumococcus type I was identified as the causative agent, type specific antipneumococcal serum would be used only in those patients who appeared to be very ill on their admission to the hospital. This plan was considered wise because of the theoretical possible advantages of the combination of two types of specific therapy, namely, serum therapy and drug therapy. In most instances the use of antipneumococcal serum in patients ill with type I pneumococcal pneumonia was on an experimental basis, the results of which will be reported by one of us (J. W. H.) in another communication.

The routine peroral dosage schedule for either sulfapyridine or sulfathiazole was as follows: Initial dose, 4.0 grams, which was given as soon as the clinical diagnosis of pneumonia was established. Then, 1.0 gram was given every four hours day and night until the temperature had been normal for 48 hours. This was followed by 1.0 gram given every six hours until resolution of the pneumonia was well under way; and finally, 0.5 gram was prescribed four times a day until the patient's lungs were clear. If, however, on the day after the institution of treatment with either sulfapyridine or sulfathiazole, the rectal temperature of the patient had not dropped to below 101° F. and the concentration of "free" sulfapyridine or sulfathiazole in the patient's blood was under 4 mg. per cent, it was our practice to give one dose of 0.06 gram per kilogram of either sodium sulfapyridine or sodium sulfathiazole by the intravenous route, the peroral administration of the drug being continued as before. Solutions of sodium sulfathiazole are prepared and administered in the same way as has previously been described for the intravenous use of sodium sulfapyridine.

The course of pneumococcal pneumonia in adult patients in The Johns Hopkins Hospital from June 20, 1939 to July 1, 1940 is outlined in table 4. It is to be noted that in contradistinction to previous years, only one patient received antipneumococcal serum alone. This exception was made because this patient had previously received sulfathiazole and had suffered from a drug rash with fever. Twenty-five patients received serum and sulfapyridine, 12 received serum and sulfathiazole, five received type specific serum and both sulfapyridine and sulfathiazole, 68 were treated with sulfapyridine alone, 66 with sulfathiazole, and 13 received both sulfapyridine and sulfathiazole. Actually, in this group of 190 patients, 20 or roughly 10 per cent, were considered to be so ill on entry into the hospital as to require intensive serum and drug therapy. Table 4 shows, furthermore, that in the entire group of patients, changes were made from sulfathiazole to sulfapyridine or vice versa, in 18 instances. In 12 of these instances the shift was from sulfathiazole to sulfapyridine and was made primarily because it was thought that the necessary drug effect was not being obtained. In four instances in which a shift was made from sulfapyridine to sulfathiazole, nausea and vomiting from the sulfapyridine were the cause of the shift, while in two instances the

by thoracentesis. The empyema fluid contained a *Streptococcus viridans*. Thoracotomy with rib resection was done during the sixth week. Twenty-six days postoperatively the patient developed signs of cardiac decompensation rather suddenly and died on the twenty-eighth postoperative day.

*Discussion:* In this case the sulfapyridine initially controlled the pneumonia, and the ultimate outcome was the result of a postoperative complication.

*Case 7.* This was a 28 year old female who had been previously hospitalized elsewhere for cardiac decompensation due to chronic rheumatic heart disease, with mitral stenosis and insufficiency. She was admitted in decompensation on the third day of a lobar pneumonia involving the right middle, right lower, and left lower lobes. The sputum contained a pneumococcus Type VIII. The blood culture was negative. The temperature dropped from 104.8° F. to 99.0° F. in 56 hours after sulfapyridine therapy was instituted. There was a leukocyte response from 9,500 on admission to 21,000. However, the decompensation progressed. Repeated right thoracenteses were necessary for hydrothorax, and the patient finally died a cardiac death on the thirty-first day after admission.

*Discussion:* Again in this case the drug exerted an initial beneficial effect, the patient ultimately succumbing to a condition unrelated to her pneumonia.

*Case 8.* This patient was a 55 year old male with hypertensive cardiovascular disease and diabetes, who had been chronically decompensated for six months before this admission. The sputum contained a pneumococcus Type III. The blood culture was not taken. Roentgen-rays showed a consolidation of the left lower lobe. The patient was given a total of 30 grams of sulfapyridine for a period of six days beginning on the first day of his illness. The leukocytes rose from 8,700 to 11,100. There was a good clinical response, and convalescence was uneventful for 10 days. He was being allowed up when he gradually became decompensated again, on the twenty-eighth day suddenly developed signs of a cerebral thrombosis with a hemiplegia, and died two days later.

*Discussion:* In this case also there was a good therapeutic result from the use of the sulfapyridine in the treatment of the pneumonia. However, the additional load was too much for an already severely damaged heart to bear and following the development of the decompensation a cerebral thrombosis developed which eventually led to the patient's death.

#### CASES FAILING TO SHOW A GOOD CLINICAL RESPONSE

As noted in the introduction, in addition to the eight patients who died, there were seven cases who failed to show a good clinical response to the use of sulfapyridine in the treatment of pneumonia, but who eventually survived. Brief summaries of these seven cases follow.

*Case 1.* This patient was a 59 year old female, whose sputum contained a Type XVII pneumococcus. The blood culture was negative. The roentgen-ray showed a consolidation of the right middle and right lower lobes. She was given 42 grams of sulfapyridine, starting on the fifth day of her illness, and the white blood count rose from 34,000 to 53,400. However, the drug failed to affect the course of the

TABLE IV

The Course of Pneumococcal Pneumonia in Adult Patients in the Johns Hopkins Hospital from June 20, 1939 to July 1, 1940

Type	No. Cases	Admission Bacteremia	No. Cases Treated with							Incidence of Complications	Incidence of Concurrent Disease	Drug Toxic Reactions	Case Fatality Rate
			Serum	Serum S.P.	Serum S.T.	Serum S.P. S.T.	S.P.	S.T.	S.P. S.T.				
1	40	11	1	20	6		6	5	2	7	11	8	
2	9	1			1	1	2	4	1	2	2	3	
3	20	1			2	1	7	6	4	2	7	6	3
4	7	1				1	1	5					.1
5	6	1		1			1	4		2	1	1	
6	1						1				1	1	
7	20	2		2	2		6	7	2	2	6	3	1
8	18	3		1	1	1	7	7	1	1	7	4	1
9	4						4				4		1
10	2						2				2	1	
11	5						5				3		1
12	4	1					1				1	1	
14	3	1		1				3			1		1
15	2						2	2			1		
16	1						1	1			1		
17	1					1					1		1
18	7	1					2	5		1	1	2	
19	2						1	1	1		1	2	1
20	3						2	1			2	1	1
21	1						1						
22	5						2	3			3	2	
24	1						1	1			1	1	
25	4							3			2		
27	1						1	1			1		
28	1						1				1		1
29	1						1				1		
Un-typed	21	1					14	5	2		9	2	1
Mixed 3 & 8		1					1						1
Total	190	25 or 13.2%	1 or 0.5%	25 or 13.2%	12 or 6.3%	5 or 2.6%	68 or 35.7%	66 or 34.7%	13 or 7.0%	15 or 7.9%	69 or 36.3%	38 or 20.0%	15 or 7.9%

shift was made because good response to sulfapyridine therapy had not been obtained.

Fifteen deaths occurred in the group of 190 patients, thus giving a case fatality rate of 7.9 per cent, which compares very favorably with that of 7.2 per cent noted during 1938-39. Eight of the deaths occurred in the group of patients treated with sulfapyridine, whereas one patient died in the group treated with sulfathiazole alone. Three of the patients treated with both sulfathiazole and sulfapyridine died, and there were two deaths in the group that received sulfapyridine and serum, and one in the group that received both drugs and serum. We do not think that the high percentage of deaths in the patients treated with sulfapyridine represents a lesser therapeutic effect of sulfapyridine, but believe that these deaths were distributed by chance. In contemplating the deaths which occurred in our group of patients, in six instances death resulted primarily from a major concurrent disease, in seven instances death took place within 12 hours after therapy had been instituted, and in but two patients did death occur despite seemingly adequate treatment.

The observation that seven patients died within 12 hours after treatment had been started brings most forcibly into the foreground the necessity for

The multiple distortions and the strain of supportive soft tissues caused by weak feet should be given adequate consideration in all stages of arthritis. Such strain causes fatigue and is an important factor in increasing the disability in the ambulatory stage of arthritis. The anatomical alignment of the superstructure (the trunk) is dependent upon the sturdiness of the foundation (the feet). Figure 10 shows the normal weight-bearing line<sup>25</sup> in the lower extremities, while figure 11 is the same patient before her

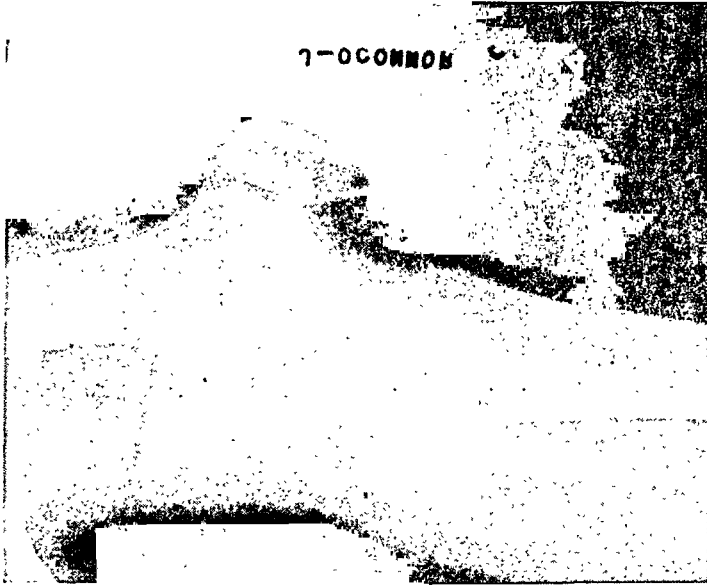


FIG. 9. Roentgen-ray of tibial dislocation shown in figure 8.

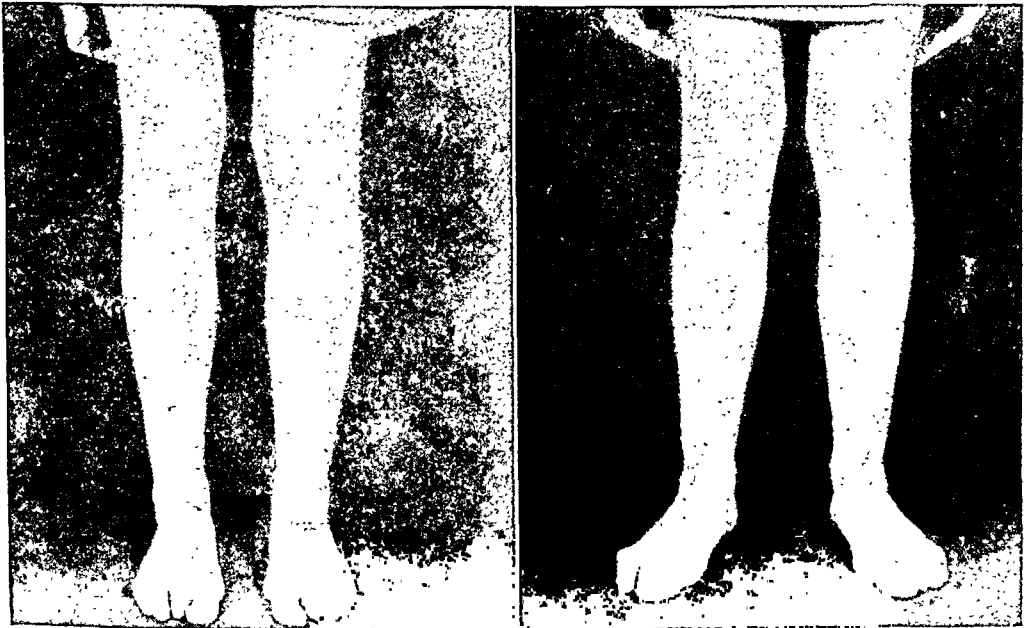


FIG. 10. (Left) Patient with normal weight bearing line.

FIG. 11. (Right) Weak feet cause strain on tarsal and ankle joints and result in knock knees.

weak feet had been corrected. It will be seen in the latter picture that the eversion and valgus of the feet caused a strain<sup>26</sup> on the ankle and tarsal joints. In addition, the eversion precipitated bilateral knock knees with the resultant strain on the internal lateral ligaments and capsules<sup>27, 28</sup> of the knee joints. It is readily seen that in the early stages of the disease the traumatic irritation caused by these distortions provides a fertile field for the advancement<sup>22</sup> of rheumatoid arthritis. Again, when the patient bears weight following acute attacks, the soft tissue strain retards the subsidence of the inflammation in joint tissues.

The treatment for the correction of weak feet is tedious, but not difficult. While the feet are still malleable, treatment should be started by strapping the feet in dorsi-flexion and inversion for a period of 10 days. Then foot plates (if needed) and correct shoes are worn. Corrective exercises and attention to proper walking posture complete the treatment.\*

In the wrists and hands the deformities to be guarded against are flexion and ulnar deviation (figure 12) with hyperextension at the proximal interphalangeal joints. The method of preventing deformity, in the wrists and fingers consists of complete immobilization during the painful stage followed by the use of a removable anterior splint, such as is shown in figure 13.



FIG. 12. (Left) The early distortion in wrists and fingers.

FIG. 13. (Right) Molded splint to prevent the deformity seen in figure 12.

This splint extends from the elbow to the fingertips and is slightly "cocked up" at the wrist. A flange on the ulnar side prevents ulnar deviation. Active use and appropriate physical therapy<sup>29</sup> can be used in conjunction with the splint.

In cases in which measures of prevention are not instituted, deformities begin to develop early. The first sign of oncoming deformity is the inability, at examination, to place the joint in the position opposed to the deformity. For example, in the case of the wrist and the hand, when the doctor finds that full extension and radial deviation are no longer present,

\* For details of treatment for weak feet see Anopol<sup>30</sup> and Stump.<sup>25</sup>

the early treatment of pneumonia. It is possible that if these seven patients had come to the hospital early in the course of their illness, death would not have occurred.

Another factor of considerable importance is the adequacy of treatment. Not infrequently during the past year we have observed patients who had been treated with sulfapyridine for several days before coming to the hospital. On entry these patients all showed frank signs of pneumonia, but in general the symptoms of their disease were somewhat masked, and they had been sent in to the hospital because it was thought that they had not responded favorably to sulfapyridine therapy. On questioning such patients, it was learned frequently that they had had inadequate amounts of the drug, sometimes not more than three tablets (1.5 gm.) per day. *We cannot stress too strongly the need for the early, intensive, specific treatment of pneumonia if the case fatality rates in this disease are to be materially reduced in the future.*

We<sup>5</sup> have already shown that following the administration of single peroral doses of sulfathiazole the blood levels of the drug generally rise quite quickly, and in the absence of impaired renal function, the drug disappears from the blood more rapidly than has been noted either with sulfanilamide or sulfapyridine. Sulfathiazole is acetylated in the tissues to about the same degree as has been previously noted for sulfanilamide. It is possible that more of the drug would be acetylated if it were not excreted from the tissues so rapidly. Sulfathiazole is distributed fairly evenly in the tissues and it seems to pass over into infected pleural fluids readily. However, our experience leads us to believe that it does not pass over readily into the spinal fluid. The drug is almost completely excreted in the urine in which the conjugated fraction (acetyl sulfathiazole) constitutes a lower percentage of the total drug excreted than is generally the case with either sulfanilamide or sulfapyridine. Not infrequently in the urine one finds crystals of acetyl sulfathiazole. *These crystals unless accompanied by hematuria are of no significance.* Because of the rapid excretion of the drug, it is necessary to follow a four-hour dosage schedule. If the interval between doses is greater than four hours, the maintenance of adequate concentrations of the drug in the blood of adults becomes increasingly difficult. In certain patients even when using the dosage schedule which we have previously outlined, it has been difficult to maintain therapeutically effective concentrations (4 to 6 mg. per cent) of sulfathiazole in their blood. In such patients accessory therapy with solutions of the sodium salt of sulfathiazole given by the intravenous route has been necessary. These observations on the absorption, excretion, diffusion and acetylation of sulfathiazole in man have been confirmed and extended by Reinhold et al.<sup>6</sup> and especially by Sadusk and his associates<sup>7</sup> whose extensive observations beautifully outline the clinical pharmacology of sulfathiazole.

During the past year, the number of patients who were ill with pneumococcal pneumonia and treated with either sulfapyridine or sulfathiazole

Asymmetry of the shoulders may be caused by a scoliosis or a functional curve of the spine, or by muscular paralysis, atrophy or swelling. A scoliosis is rarely present with symmetry of the shoulders. At this point in our examination we need note only whether or not there is asymmetry and, if there is, determine whether there is atrophy or swelling. Paralysis will be determined later on. Swelling as the sole cause of asymmetry is rare but, if present, tumors are to be suspected. Atrophy, especially of the supraspinatus, should be searched for; it is most frequently due to disuse following an in-

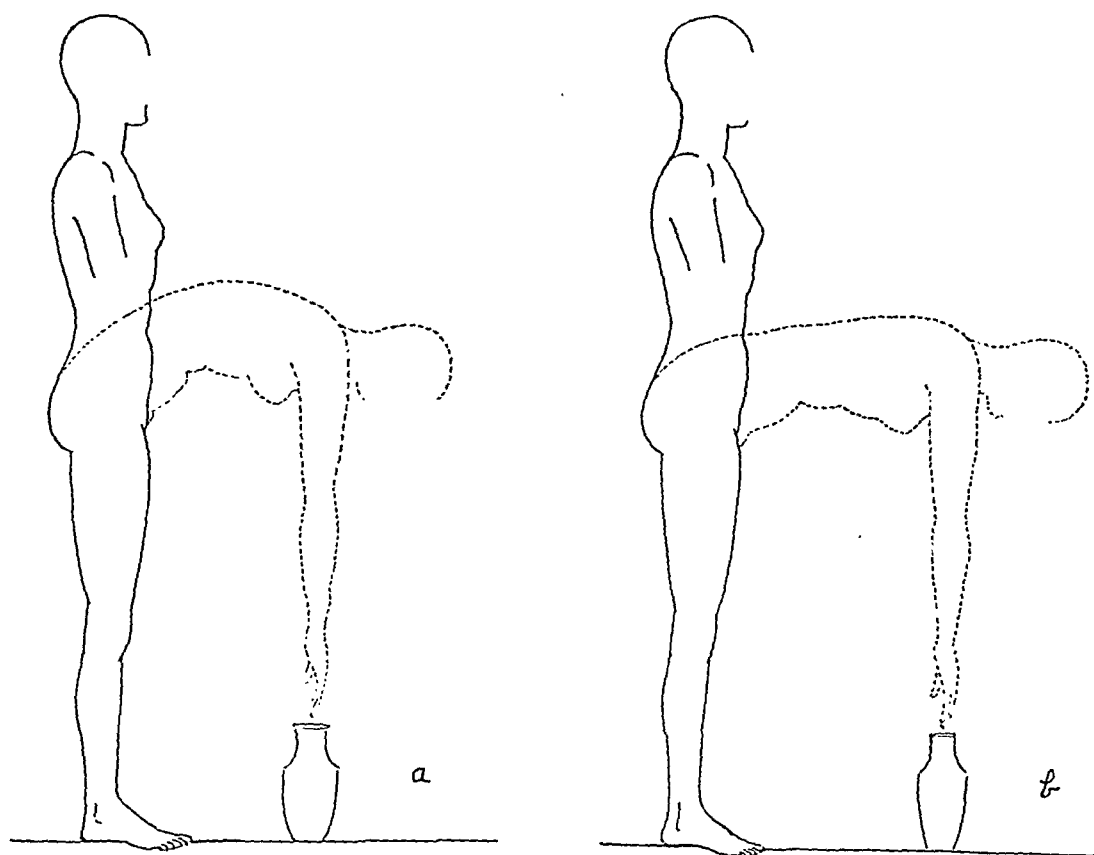


FIG. 3. *a.* Hip flexion limited and spinal flexion added. *b.* Hip flexion.

jury to its tendon. Atrophy of the deltoid is usually due to paralysis either of the muscle itself, or of other muscles, which causes its disuse.

If the elbows go into hyperextension, there is ligamentous relaxation and this condition may be found to be quite general throughout the joints. Probably at one time, if not now present, there was faulty metabolism on the order of rickets.

A pelvis which is inclined laterally is most frequently associated with some condition of the lower extremities making one leg shorter than the other, but it may be due to bony deformity or paralysis or myositis in the lumbopelvic region. Shortness of one leg may be due to any of the follow-

has not been sufficient to provide a true comparison of the toxic effects of these drugs. However, the incidence of drug rash and drug fever was significantly more common in those patients treated with sulfathiazole than it was in those who received sulfapyridine. This observation is in line with that previously made by us in a series of 300 patients suffering from miscellaneous diseases and treated with sulfathiazole. Hence it is permissible to conclude that these two reactions, fever and rash, are far more prevalent in the course of sulfathiazole therapy than when sulfapyridine is used. Injection of the conjunctivae and sclerae, which constitutes a new type of toxic reaction and which to date has only been observed in patients receiving sulfathiazole, occurred twice in this group of patients. Granulocytopenia was noted in one patient. No instances of acute or mild hemolytic anemia were seen. Hematuria, either microscopic or gross, occurred about as frequently in the patients treated with sulfathiazole as it did in those who received sulfapyridine. Nausea and vomiting of a moderate or severe grade were relatively infrequent in the patients who were treated with sulfathiazole. Three patients in this group developed oliguria and anuria in the course of therapy with sulfathiazole. In these patients, following the forcing of fluids, kidney function was restored and the patients recovered.

### DISCUSSION

Our experience with the use of sulfathiazole in the treatment of pneumococcal pneumonia leads us to believe that it is as effective a chemotherapeutic agent as is sulfapyridine. One definite advantage is that sulfathiazole produces less nausea and vomiting in adult patients than does sulfapyridine. This is a point of considerable importance, especially when the treatment of pneumonia in the home is taken into consideration. From the information which is now available, it seems that while sulfathiazole produces more instances of drug fever and drug rash, it rarely produces anemia or granulocytopenia, and so far, we have not encountered patients who developed agranulocytosis in the course of therapy with this drug.

We are of the opinion that the importance of early treatment of pneumonia by chemotherapeutic agents has not been sufficiently stressed, and that every effort should be made to use either sulfathiazole or sulfapyridine as early as is possible in the course of pneumococcal pneumonia. Adequate doses of these drugs should be used, because otherwise unsatisfactory therapeutic results will be obtained.

At the present time we feel that every patient who is severely ill with pneumonia should receive combined type specific antipneumococcal serum therapy as well as chemotherapy. The administration of serum should, when it is possible, be controlled by the Francis skin test. If this is not possible, an initial dose of 200,000 units of type specific serum should be given to patients by the intravenous route after it has been determined that they are not sensitive to the particular kind of serum which is to be employed.



ing conditions: changes in the position or shape of the acetabulum; dislocation of the head of the femur; changes in the shape of the head of the femur; tuberculosis, Perthe's disease, epiphysitis, arthritis or traumatism; lessening of the angle of the neck with the shaft (coxa vara); interference with normal growth of the femur or tibia from paralysis, osteomyelitis or traumatism; deformity of the knee following traumatism or disease of that joint; unilateral flat-foot, when the everted and abducted foot may lower the head of the astragalus and the scaphoid one-half or three-quarters of an inch. An apparent shortening of the leg may be due to adduction deformity of that hip or abduction deformity of the opposite hip. If, in palpating the great trochanters, the one on the lower side of the tipped pelvis seems to be nearer the anterior superior spine, the cause is probably to be found in the neck or head of the femur.

### TRENDELLENBERG'S SIGN

When standing on both legs the center of gravity passes through the center of the pelvis and falls between the feet. If one foot is raised from the ground, the pelvis tilts downward on that side, unless the plane of gravity is shifted to pass through the one supporting leg or unless force is used to overcome gravity. Normally the gluteus medius supplies this force and holds the pelvis to its position, preventing its tipping by keeping the ilium in its normal relationship to the great trochanter. When the pelvis does tilt downward on the unsupported side, there is faulty functioning of the gluteus medius muscle of the opposite side, intrinsic, as in paralysis, or because of its attachments being brought nearer together and its contraction thereby being less effectual, as in a dislocated hip or a severe coxa vara. There is also a downward tilting of the pelvis, similar to the Trendellenberg's sign, in the presence of a painful hip, but accompanying it there is a well marked shifting of the body to the side of the supporting hip. The body is thus shifted to relieve painful stretching of the capsular ligament. It is due to a reflex spasm and is present whenever the foot on the opposite side is non-weight-bearing. When this sign is found, in the case of a short leg, we must not overlook the possibility of coxalgia, in which case leveling the pelvis will not eliminate the limp.

Although exact measurements will be taken later on to determine the presence of atrophy of the thighs or legs, it is well to estimate this with the eye.

Carefully inspect the feet. If the forefoot is abducted, i.e., turned outward through the vertical axis at the mediotarsal joint, the weight of the body must fall to the inner side of the foot, tending to evert the foot, roll it downward and outward on a longitudinal axis passing through the subastragaloid joint and to increase the abduction. This will cause lessening, or sometimes obliteration, of the anteroposterior arch and even a bulging at the astragaloscaphoid joint. Extension of the toes at the metatarsophalangeal

Then, 100,000 units of serum should be administered at eight-hour intervals until crisis occurs. Our experience during the past two years in the Johns Hopkins Hospital leads us to believe that 10 to 15 per cent of the patients entering our hospital will require combined sero- and chemotherapy. It is probable that fewer patients will need the combined therapy if in the future specific treatment is started earlier in the course of the disease.

### CONCLUSIONS

1. Over a period of two years the case fatality rate of pneumococcal pneumonia in adults has been reduced by two-thirds at The Johns Hopkins Hospital. It seems to have been stabilized at between 7 and 8 per cent.
2. Sulfathiazole and sulfapyridine seem to be equally effective in the treatment of pneumococcal pneumonia in adult patients.
3. Sulfathiazole causes less nausea and vomiting than does sulfapyridine.
4. Patients who are severely ill with pneumococcal pneumonia should receive both type specific serum and either sulfathiazole or sulfapyridine.

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joints with flexion at the first interphalangeal joint usually has its origin in overcontraction of the extensors, and the deformities are further fixed by contractures of the lateral ligaments later on. These overcontractions of the extensors arise from their efforts to flex the tibia on the foot when move-

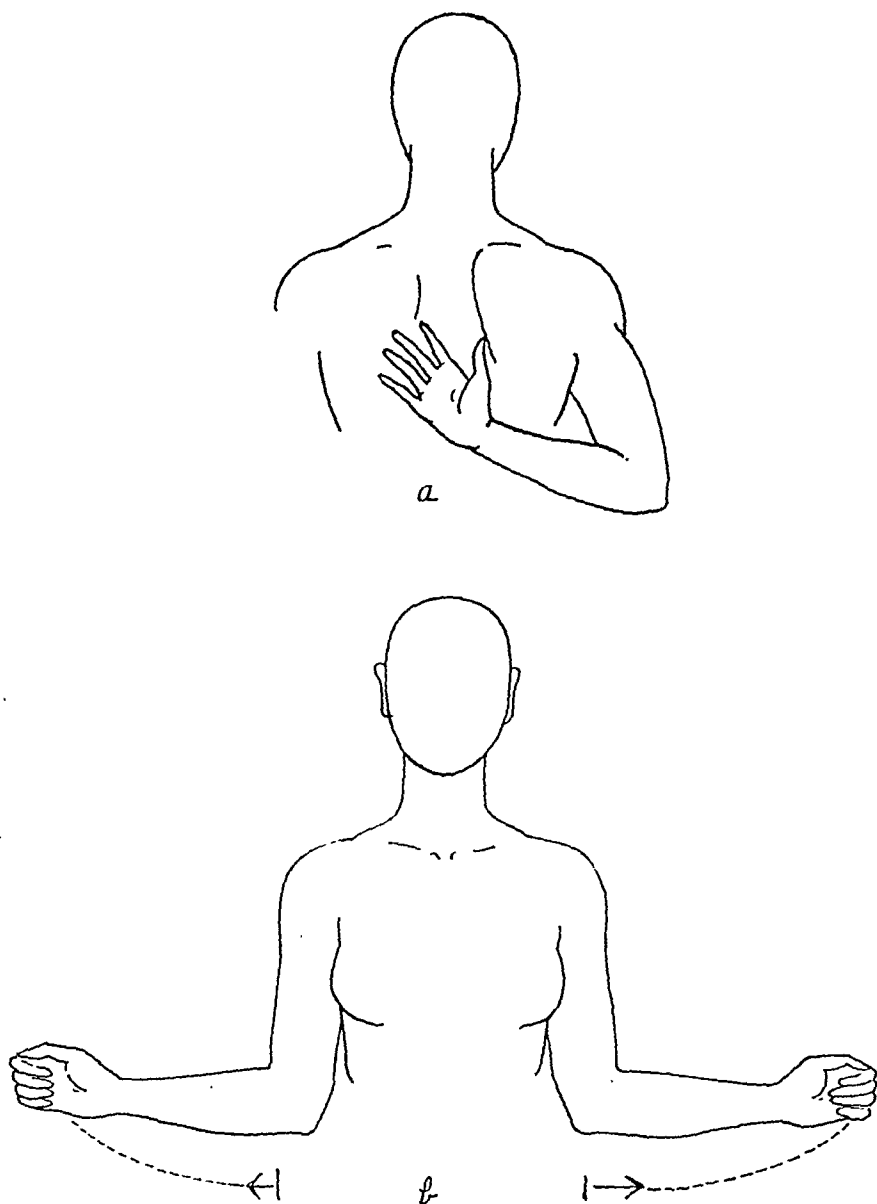


FIG. 4. *a.* Testing internal rotation of the shoulder. *b.* Testing external rotation of shoulder.

ment at the ankle joint is limited by a shortened heel cord. Enlargement of the great toe joint is very common and is caused in most cases by traumatism resulting from abduction and eversion of the foot. Observe the movement of the feet as the patient comes up on tiptoe. Does he use the mediotarsal joint or only the ankle and metatarsophalangeal joints?

## EARLY SIGNS OF ORTHOPEDIC CONDITIONS \*

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BELIEVING that few physicians other than orthopedic surgeons pay more than the slightest attention to the body mechanism, the writer deems it worth while to present a paper on the early signals of abnormalities in the framework of the body and their significance. If what is here offered to the profession serves to quicken the family physician's powers of observation, in the writer's opinion, at least, it will not have been written in vain.

Many orthopedic conditions manifest their presence by sending out some faint signal long before subjective signs draw them to the attention of the patient, and if these conditions are discovered by the physician the patient may be saved from a long illness and the loss of some joint function or a deformity. Furthermore, the condition of the framework of the body may have much to do with the general physical condition. For instance, the recognition of a faulty posture and its correction may be of great assistance in clearing up some faulty condition of the chest or abdomen.

No sensible physician would attempt to minimize the importance of roentgen-ray machines, pathological laboratories and machines for taking blood pressure, pulse tracing and metabolism rate as aids in making diagnosis; but, since the development of these valuable aids, have not our powers of observation become somewhat dulled from disuse? At the turn of the century the leaders of our profession were known to be men of keen observation, and few of the signs given by Nature escaped their highly trained senses. A very clever internist might be 24 hours ahead of his colleagues in recognizing a pathological condition, and an experienced surgeon would be able to mark out the line of a fracture so exactly that his findings could scarcely be improved upon by a roentgen-ray. The all-seeing eye, the sensitive finger, the trained ear and, I might add, the knowing nose are still most helpful instruments in making diagnoses.

Begin your critical observation as the patient enters your consultation room. He will usually assume his best position, as we naturally do upon making a new acquaintance, but a poor posture resulting from a bony lesion cannot easily be hidden, nor can an ingrained habit of poor posture be readily changed. Shake hands with the patient and notice the temperature of the skin and the degree of moisture. A cold, damp hand is usually indicative of a faulty sympathetic nervous system. The expression of the face and eyes, especially the eyes, is replete with signs for the physician if he will but recognize them. The look of apprehension in the eyes of the arthritic patient is very familiar to the orthopedic surgeon, as is the look in the eyes of the child with Pott's disease—a look which the bravest smile can not dispel.

\* Received for publication April 19, 1940.

The patient is now seated and the examiner pulls a stool up for himself. The stool must be of such a height that, as he sits at a right angle to the patient, the patient's leg can rest comfortably across the examiner's knee. Before beginning the examination of the knee test the patella reflex. Then, with the patient's leg resting as above described, look for redness, heat and swelling. Test the patella for evidence of synovitis and, if doubtful as to the presence of swelling, compare the knees in the same position; or it may seem advisable to measure the circumference of the knees in the same horizontal planes. With the knee completely relaxed, the patella being freely movable from side to side, the knee is passively flexed 15 or 20 degrees and then smartly extended. Is there any resistance to the movement? Does the knee spring back to a few degrees of flexion? Does the patient wince or complain?

A localized area of heat about one knee demands an explanation. It may be present although there is no redness and very slight swelling. If there is no apprehension of the knee joint in passive extension internal derangement can usually be ruled out. If there is resistance to full extension, or if the knee springs back into flexion, there is either an inflammatory condition (arthritis, synovitis or bursitis) or injury to a cartilage. A slight resistance, comparable to that of an elastic tissue, may be encountered in shortening of the gastrocnemius muscle.

In the normal knee there is no lateral movement with the joint in full extension. If lateral movement is present it is due to ligamentous relaxation, and faulty metabolism should be suspected. The lateral ligaments may have lost their strength through a disease (Charcot's joint) or through traumatism. Lateral movements with the knee flexed to about 135 degrees will test the condition of the lateral ligaments. In this position these ligaments are relaxed and, if sprained, pain will be felt when they are stretched. Bone injuries to the condyles or tuberosities will cause pain when the knee, in this semiflexed position, is so moved as to make pressure on the point of fracture. In the presence of an acute injury to a lateral ligament, pain will be excited by pressure over its bony attachment. Pain on pressure over a semilunar cartilage is usually an indication of injury to that cartilage. Palpation of the entire knee may reveal a latent condition, such as a bursitis or a cyst, and palpation of the tibial tuberosity will always reveal the presence of Osgood-Schlatter's disease.

Pain on pressure over the tibia reveals periostitis. This may be an indication of syphilis or osteomyelitis; or it may be a traumatic periostitis caused by the pull of a muscle on its periosteal attachment. It should be noted whether or not any pain is bilateral and whether or not it is accompanied by local heat. Any bony swelling, even though very slight, demands further investigation. Pitting on pressure along the length of the tibia may be an indication of circulatory or nephritic disturbance.

A difference in the color of the foot on the physician's knee and the one

The face quickly reflects the presence of pain or ache, and the good diagnostician is adept at interpreting the facial expressions of his patients. Too frequently perhaps, if we are impressed by something but can not seem to connect it with the condition for which we are looking, we consider it simply a "hunch" and dismiss it as of no scientific value. Observe the patient as to freedom of movement—movement of the head and neck, shoulders, elbows, hands. Does he show any awkwardness in sitting and has he any difficulty in finding a comfortable position? Is there free movement of the spine as he bends forward or to one side in the course of conversation? Keep in mind that a patient may be badly crippled in a joint and be scarcely aware of it. A keen eye will note that he moves that joint very little, that its functions are taken up by other joints. The hands are very revealing. During the taking of the history they can be scrutinized for color, suppleness and swelling. Notice also the condition of the nails. The symptoms which the patient relates may not suggest a cardiovascular lesion or a glandular dysfunction or arthritis, but if the physician finds signs that point to these conditions they must not be ignored even though it may seem inadvisable at the time to advise the patient of what has been found. A slight, painless, lateral deformity at the distal interphalangeal joint, perhaps an insignificant nodule, will disclose to the doctor the presence of hypertrophic arthritis; or a slight spindle-shaped enlargement of the second interphalangeal joint, noted by the patient only as a stiff and slightly aching joint, will give warning of the presence of atrophic arthritis; or the nails may show marked unevenness, ridges, or thickening, and the possible presence of a glandular dysfunction or avitaminosis must be borne in mind.

The history finished, the patient is asked to go into another room, to take a seat, to remove his coat and shirt or to do whatever is necessary to make an examination of that part of the body from which his complaint seems to arise. Observe the way he arises from a sitting position, whether with alacrity or with care, pushing himself up with his hands on the chair-arms. The latter is a sign of stiffness or pain or weakness. Usually it points to both pain and stiffness in the hip joints or the lumbar spine. As he stands up, glance at his feet. Are they parallel or pointing outward? Feet that point outward are usually weak feet and, conversely, feet that point straight ahead, forming a square, are usually strong, even though they may not always be exactly normal.

An examination of the posture can be made in a few minutes, before the patient undresses for whatever examination is to be made; and if it is found to be quite normal that information is of value, whereas any abnormalities that are brought out will be considered in relation to the symptoms from which the patient suffers. No patient will object to a quick survey of his stance, particularly if it appears to be a matter of routine. Make a survey of the patient's back, noting the symmetry of the shoulders; place your thumbs on the inferior angles of the scapulae and note if they are on the

hanging down hints at a possible abnormality in the peripheral circulation. A good test of peripheral circulation is to note how rapidly the color returns to normal after deep pressure with a finger. The dorsalis pedis and the posterior tibial arteries should always be examined for patency.

The examination of a foot begins with palpation to discover any areas of swelling, heat or tenderness, and any signs of synovitis from chronic strain, as from weakfoot, or of early arthritis. The lateral ligaments at the ankle are seldom painful on pressure except after a severe traumatism. The suspensory ligament (the calcaneo-scaphoid ligament) is frequently painful in abducted feet. Pain on pressure over the calcaneocuboid joint is also frequently found, caused by a traumatic arthritis excited by forced abduction. Callosities are very informative of abnormal use of the foot. Callosities under each of the metatarsal heads are pathognomonic of limited dorsal flexion at the ankle. Callosities on the lateral side of the fifth metatarsophalangeal joint and on the dorsal surface of the first interphalangeal joints of the two outer toes are produced by pressure of these areas against the shoe leather, caused by the pronation of the foot. A callosity on the mesial side of the first metatarsophalangeal joint is a sign that the pressure which should be dispersed over the entire plantar surface of the forefoot is being received at this joint because of the eversion and abduction of a flat foot, with the mesial side of the joint rolled to a position more in contact with the ground. A narrow pointed-toe shoe adds to the pressure on this joint, as does the deformity of hallux valgus. This pressure may be great enough to cause a traumatic arthritis, which frequently results in an exostosis, and Nature, in her endeavor to protect the joint, produces a bursa. Callosities around the edge of the heel are common in "heel-walkers," the whole weight of the body being thrust down through the heel at each step.

Dorsal flexion at the ankle should be to 85 degrees with the leg. If this is 90 degrees or more the foot cannot function normally. In walking, the movement at the mediotarsal joint is limited by the height of the heel worn; the higher the heel the less movement is there at this joint. When standing, it is not necessary for the foot to be at a right angle with the leg, but the higher the heel the less free is the mediotarsal movement and the greater the weight thrown on the forepart of the foot.

In spasmodic flat foot adduction is markedly limited. The spasm is in the peroneal muscles and is caused, reflexly, by the traumatic arthritis of the mediotarsal joint, which is itself caused by using the foot in an abducted and everted position. It must be borne in mind that this peroneal spasm is present in any arthritis of this joint and may be infectious in nature.

Deformities of the toes are found frequently. When these are not fixed but are easily corrected by manipulation we may prognose their cure by the correction of the faulty mechanics of the foot which usually exist. Long-standing deformities of the toes, such as hammer-toes, are generally fixed by shortening of the lateral ligaments, shortening of the tendons, and

same level and at the same distance from the spine; place the hands under the axillae and, moving them downward over the hips, compare the waist-lines; ask him to bend forward as though to touch the floor and notice if the bending seems to be free in both the hips and spine. While he is thus bent over, place the hands on either side of the spine, high up in the dorsal region and, drawing them downward to the pelvis, using slight pressure, feel for any asymmetry. From the side of the patient, move the hand

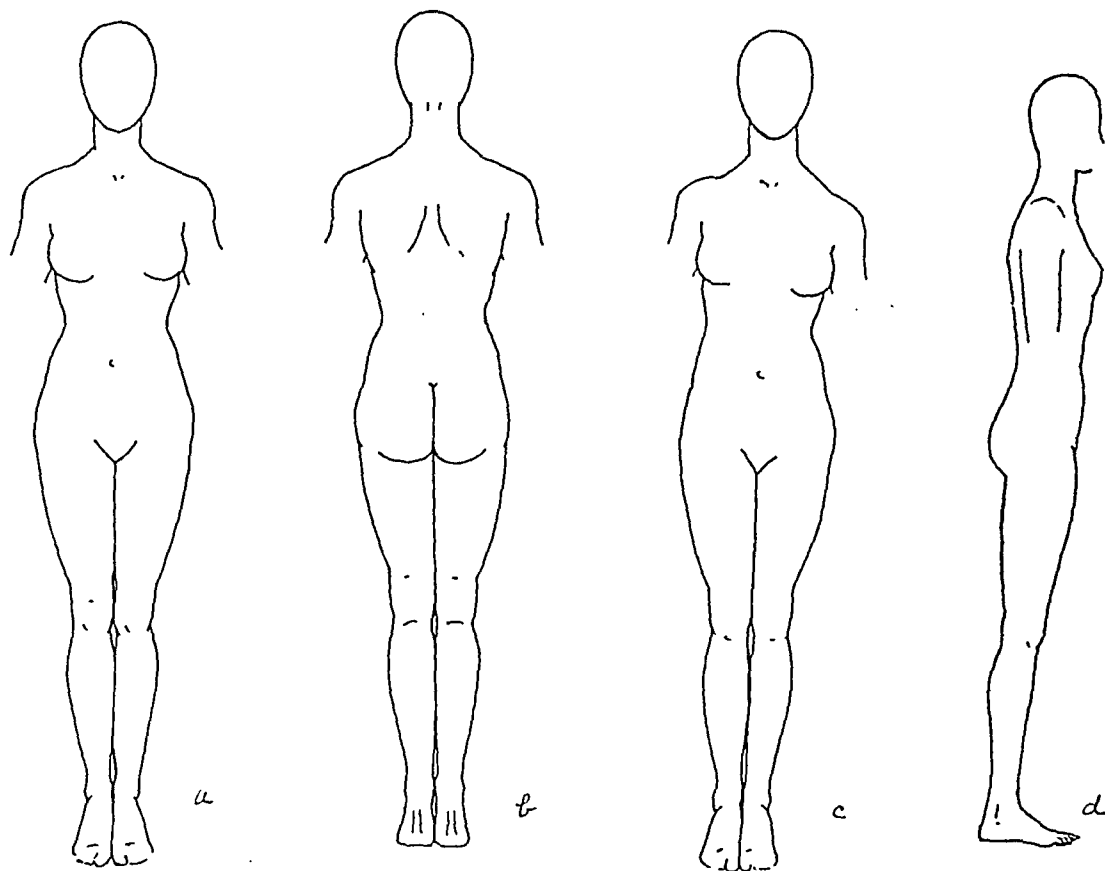


FIG. 1. *a* and *b*. A vertical line through the center of the body should divide it into exactly symmetrical parts. Any differences in lines, creases, prominences must be noted. *c*. Asymmetry of neck, shoulders, breasts, waist line, inguinal folds. *d*. Lateral view of a good posture.

down the length of the spine to estimate the normality of the anteroposterior curves and, with the other hand, note whether the abdomen is prominent or flat. Stooping in front of the patient or sitting on a stool, place the thumbs on the anterior superior spines and with the fingers grasp the great trochanters. Note if the thumbs are on the same level and if the trochanters seem to be in the same relative positions to the spines. Have him place his feet together and slip your hand between the knees. Do they come together or are they separated, and to what degree? Finally, have him rise on tiptoe. Does he throw the heel outward, flexing the mediotarsal joint,



sometimes by deformities of the metatarsal heads. There may be a very limited range of motion, or even no motion, in the first metatarsophalangeal joint. This is called "hallux rigidus" and is a very serious condition, because it interferes greatly with the use of the foot.

Hallux valgus, usually associated with flat-foot, if correctable with the hand, may be greatly improved by correcting the flat foot. However, if there is marked deformity with much new growth of bone it must be operated upon.

The examination is completed with the patient on the table. Normally, with the patient lying on his back with knees drawn up, the lumbar spine



FIG. 5. Patient lying supine on the table. The heel of one foot is brought upward toward the groin on the other side. This tests flexion, abduction and external rotation of the hip.

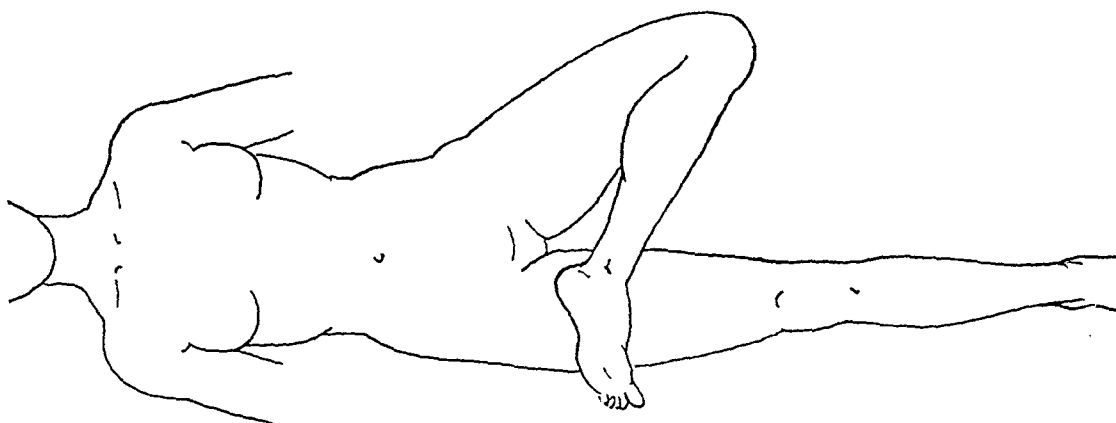


FIG. 6. If the heel of one foot advances higher up toward Poupart's ligament than the other heel, then there is a difference in the two hips.

flattens out, going into a slight curve when the hips are extended. To test the hips for flexion deformity, have the patient draw up the right knee and press it firmly against the abdomen, thus holding the lumbar spine against the table. If the left hip does not go into flexion there is no flexion deformity at that hip; in the presence of such a deformity the leg will rise from the table. Both hips should be tested in this way, as both may be so deformed though perhaps not to the same extent. Bringing the heel of one foot up to the opposite groin puts the hip through flexion, external rotation and abduction. Very early in an arthritis of the hip one or more of these movements is limited.

Straight leg flexion of the hip is of value in detecting strain at the sacroiliac and lumbosacral joints. The straight knee, tightening the ham-

or does the movement seem to be confined to the metatarso-phalangeal joints? At the time it may seem inadvisable to pursue any abnormalities revealed in this examination, but they should be entered in the history and when an opportune time arrives examined thoroughly and the exact cause ascertained.

In making an examination with the clothing removed, whether the patient is an adult or a child, modesty must always be respected. If the body is kept covered except for the part under immediate scrutiny, the patient will be more comfortable and, therefore, more relaxed, and thus the physician's work is facilitated. For an examination of the posture a small sheet pinned around the neck and draped over the front of the body and a sheet pinned around the waist and draped about the legs will be found adequate.

First, with the patient standing, examine the back. Observe the symmetry of the curves of the neck, the shoulders, the scapulae and the waist-lines, not only as to longitudinal planes but as to development as well. Asymmetry in the curves of the neck may be due to a lateral curvature involving the cervical vertebrae, to a congenital abnormality, to arthritis of this region including tuberculosis, to torticollis or to cervical adenitis. If any asymmetry is noted further exploration may be left until the anterior examination has been made. Do the scapulae differ in position; is one higher than the other or further from the spine? Are they flat against the thorax or winged? If one scapula is higher than the other we suspect Sprengler's disease. If one is further from the spine than the other we expect to find paralysis or lateral curvature. Winged scapulae frequently accompany faulty posture, the depressed or lowered ribs allowing the scapulae to glide forward. They may be present also in paralysis.

The patient is now instructed to abduct both arms, continuing the movement until they are raised straight over the head. Is the movement in both shoulders the same in all respects? As they reach the horizontal position and continue upward, do the scapulae begin to rotate in unison? Have him draw the scapulae close together and then separate them as much as possible. Are these movements symmetrical? Reaching up the back between the shoulder blades, first with one hand and then with the other, does each hand ascend to the same height? With elbows bent to a right angle, have the patient swing the hands outward and backward as far as possible. Is the same length of arc described by both hands? Is abduction at the shoulder of normal range, to 90 degrees? In abduction of more than 90 degrees the scapula rotates on the thorax, carrying the arm with it; and if the scapula begins to rotate before 90 degrees is reached, there is abnormality in or about the humeroscapular joint. Inability or great difficulty to fully abduct to 90 degrees but ability to hold that position, when it is attained with or without help, shows that there is complete or partial rupture of the supraspinatus. Limited rotation at the shoulder points to bursitis, arthritis or periarthrititis; rarely to neuritis.

strings, exerts a strong pull on the tuberosities of the ischium which tends to rotate the pelvis on a transverse axis. Normally, this rotating force is communicated to the lumbar spine which, straightening its curve by extension, permits the rotation of the pelvis. If, however, the sacroiliac joint or the lumbosacral joint is strained or arthritic the force will produce pain. If there is a lesion of the sacroiliac joint on one side, straight leg flexion of the opposite hip may excite the pain. This is due to the fact that the force, after continuing through the normal sacroiliac and lumbosacral joints, flattens the lumbar curve and thus rotates the pelvis; but as the force of rotation reaches the other sacroiliac, where the trouble exists, it excites pain. Limitation of flexion of the knee may be a sign of contracture of the quadratus femoris.

Limitation of abduction may be due to contractures or spasmodic contractions of the adductor muscles or to disease of the hip joint. Spasmodic contractions accompanying cerebral paralysis may be overcome by gentle and steady force; this is not so of contractures. If there is evidence of spasm in muscles connected with other joints, as of the arm or ankle, it is safe to test the adductors of the hip; otherwise no force should be used until coxitis has been ruled out.

Any difference in the rotation of the two hips is indicative of a joint condition which should be diagnosed. It may be a mechanical interference but, until a diagnosis is made, we must always suspect arthritis.

Any difference in the length of the legs should be investigated with great care and the shortening definitely located. In the majority of cases it will be found in the upper end of the femur. If one trochanter is higher than the other the shortening is definitely in the neck or head. The history will be found very helpful in locating a shortening. A coxa vara may have originated in childhood and have given few recognizable symptoms; but a disease of the hip joint will present, or will have presented in the past, noticeable signs of its existence. Any traumatism or disease which has interfered with any of the epiphyses of the femur or tibia will usually provide signs of its having existed.

A test should be made of the strength of the flexor muscles of the hips and lumbar spine since muscular weakness has much to do with faulty posture. Active extension of the hip against resistance tests the strength of the muscles and also the sensitivity of the hip joint to interarticular pressure. The hip and the knee are flexed and the patient is told to straighten out the leg, while the examiner resists the movement, grasping the patient's foot firmly in his hand. If there is a fibromyositis of the gluteus maximus, pain may be excited along its attachments; or the patient may just feel it impossible to exert any power without complaining of pain, as shown by Nature's refusal to permit the interarticular pressure which must accompany the exertion, because of the presence of arthritis of the hip joint. When a hip is sensitive to pressure or to movement the patient will find it difficult to raise that leg from the table.

Asymmetry of the waistlines is a very important sign and for its detection both sight and touch are used. Any crease on one side should have its counter-crease on the other. Observe the gluteal folds. Are they on the same level and of the same depth and length? If one fold is shallower than the other, that hip is flexed; if one fold is longer than the other, either that hip is abducted or the other hip is adducted; if one fold is lower than the other, that leg is shorter than the other.

In examining the spine the first step is to mark the spinous processes with a pencil. A plumb line is dropped so that it falls into the intergluteal fold, thus erecting a vertical line from the center of the pelvis, and any of the marked spines which seem to be out of alignment are noted. A fairly satisfactory plumb line is easily made by attaching a small weight to a piece of string. If the waistlines are asymmetrical and the gluteal folds are not in the same plane, place under one foot a lift of sufficient height to make the waistlines symmetrical and make a resurvey with the plumb line. Have the patient bend forward and, as he does so, note where the bending occurs; whether it is only in the hip joints, or mostly in the spine, or in both hips and spine. While he is thus bent forward, stoop down and sight along the spine to discover if one side of the spine in any of its regions is higher than the other. Feeling down the sides of the spine with both hands will be of help. Again from the erect position, have him bend to one side and then to the other. Are the creases formed by this movement, as well as the movement itself, symmetrical? If forward bending is arrested at the hips before 90 degrees is reached, expect to find some abnormality of those joints or their controlling muscles. If the lumbar spine retains in forward bending the same curve as when standing upright, there is either malformation or arthritis in that region. If one side of the spine is higher than the other in this position, there is rotation of the vertebrae. In scoliosis the rotation is toward the convex side and in the functional curve, which is usually one long curve, the rotation is toward the concave side. If the curvature is straightened by leveling a tilted pelvis it is a functional curve.

If in lateral bending the patient bends freely and equally to either side, the lumbar spine is free from any inflammatory process; if the folds of the skin are exactly symmetrical, there is no curvature of the lower spine. If, when standing erect, deep folds on each side are noted there may be a spondylolisthesis.

If the boundaries of the popliteal space are more marked in one knee than the other there is probably limitation of extension of that knee. If, in standing, the knees are together while the feet are apart, ligamentous relaxation of the knees and pronation of the feet will usually be found. If the Achilles tendons extend straight down to their insertions, there is no rotation of the foot in a longitudinal axis, no eversion or inversion. If the tendons run downward and outward there is eversion of the foot. If the tendons run downward and inward there is inversion.

With the patient lying prone, place the hand over the buttocks holding the pelvis firmly to test the extension of the hips. Extension of the hip is limited very early in arthritis and therefore comparison of the arc of extension of the hips furnishes a sign of this condition in its early stage. Extension and lateral movement of the lumbar spine will reveal immobilization of this region by muscular spasm. It must be borne in mind, however, that extension relieves pressure between the vertebral bodies and, therefore, lateral motion may be freer in extension than in flexion. In the presence of strain on the ligaments attached to the sacroiliac and lumbosacral joints pain will be elicited by pressure over these joints; if there is a fibromyositis of the lumbar muscles, pressure over the lumbar region, one or two inches from the spine, will cause pain; and if there is a strain upon the interspinous ligaments, pressure upon them will cause pain. When there is an exaggerated dorsal curve these ligaments are under strain, as in adolescent arthritis of the spine.

The examination completed, the family physician must now make a diagnosis and give his recommendations for treatment. Roentgen-rays, blood examinations, skin tests and cultures will help him to perfect his diagnosis, and he must then decide whether he himself is fitted, by experience as well as by the facilities at his command, to carry out the required treatment. If any joint disease is suspected the patient should be kept in bed while additional tests are being made, particularly if the suspected lesion is of the spine or lower extremities. When the tests appear negative the patient may be allowed up, but should be examined weekly until the sign disappears or until a satisfactory reason for its presence is found. A specialist should be consulted if assurance is needed as to the advisability of ignoring any persistent evidence of abnormality.

View the patient from the side. If the head is thrust forward you may expect to find an exaggerated dorsal curve. The head is held forward to counter-balance the abnormal weight behind the transverse plane which normally contains the center of gravity. Congenital abnormality in the cervical spine more rarely causes this extension. An increased dorsal curve may be marked and confined to a few vertebrae, as a kyphosis, or one long, regular curve. If a kyphosis is present the patient will give a history of a long illness, perhaps arrested, or of an injury. If the curve is long and

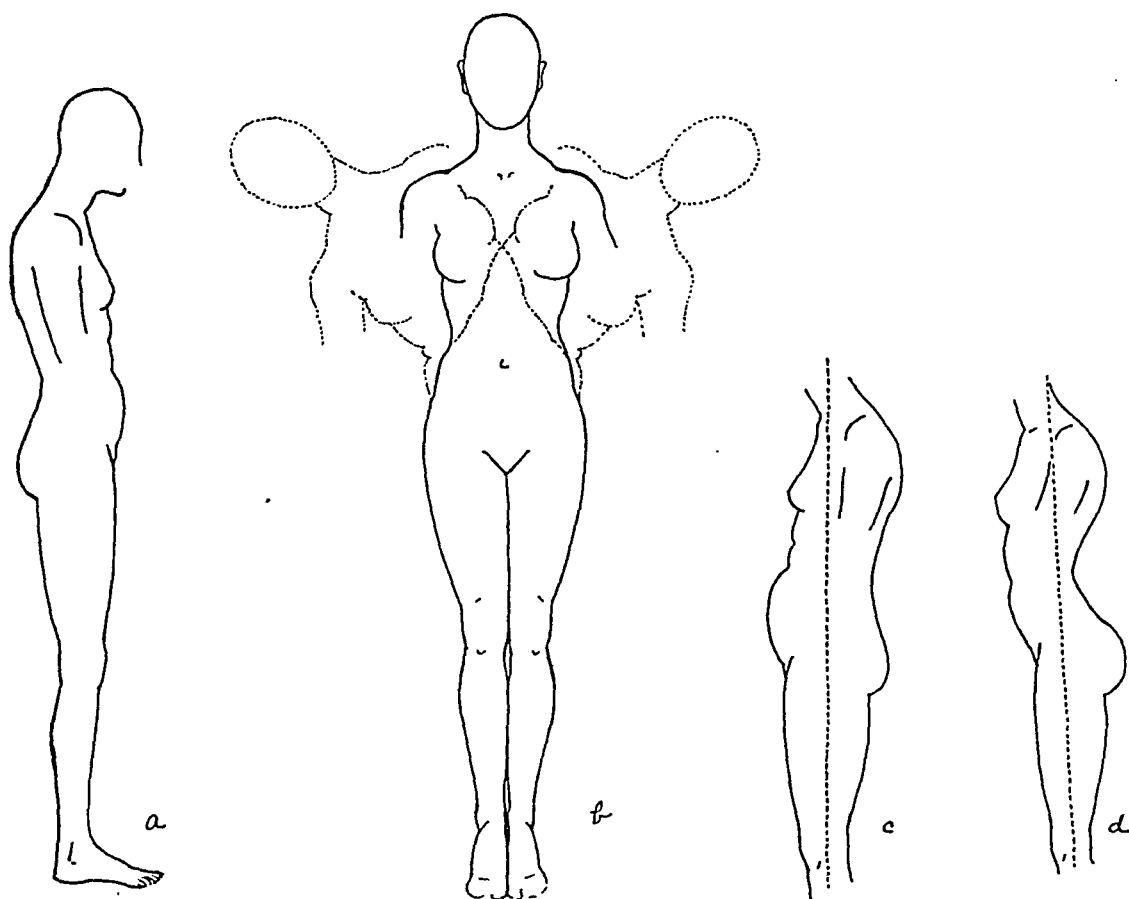


FIG. 2. *a.* Lateral view of a bad posture. *b.* Lateral bending of the spine. *c.* and *d.* Faulty postures.

regular and the patient under 20 years of age it may be adolescent spondylitis; if older it may be rheumatic spondylitis. If the curve is easily correctable it is a postural deformity. Ask the patient to take a deep breath. Is the rib expansion normal and is it rhythmical, or is there a catch or an abrupt arresting of the movement? In arthritis of the dorsal spine or of the costovertebral articulations, movements of the rib are limited by muscular spasm.

An exaggerated lumbar curve may be a postural defect due to muscular weakness, compensatory to an exaggerated dorsal curve or accompanying

# SOCIAL COMPONENTS IN MEDICINE \*

By EDWARD L. BORTZ, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

METHODS of scholarly inquiry and organized experimentation have uncovered such a mass of data bearing on man's biological and social existence that the average span of human life has been more than doubled since the 19th century. Scientific facts of importance to society are being discovered at a rate beyond the ability of society to absorb and profit by them.

## THE UNIT BIOLOGICAL

As a biological unit man has benefited by the increasing control of diseases due to contagion and infection, nutritional deficiencies and neoplasms. Typhoid fever, smallpox, and similar infections are now uncommon, and enough is known about pneumonia, syphilis and tuberculosis that, were available knowledge applied, especially of a preventive kind, these diseases would no longer represent major health hazards as is the situation today. Less than a century ago, communicable diseases accounted for approximately 900 deaths per 100,000 population per year. In order of frequency as a cause of death, these diseases were: tuberculosis, pneumonia, scarlet fever, typhoid fever, diphtheria, whooping-cough, measles and smallpox. Except for tuberculosis and pneumonia, all of the other infections have been almost entirely eliminated as important mortality factors. In 1936, less than 4 per 100,000 population died of these other infections.<sup>1</sup>

Special programs organized on a national scale and energetically carried out by the medical profession will exercise a telling effect in the control of syphilis and tuberculosis. Careful search for the early manifestations of cancerous lesions will uncover disorganized growths in the human body at a time when their complete removal will save many lives. As a biological unit, man has profited generously by the march of science.

Only recently attention has again been directed to the mind-body question. Psychosomatic problems are being more and more subjected to orderly study and classification. With an increase in the span of life and with more exact methods of scientific study, these problems of individual and social existence take on a new meaning.

## THE UNIT SOCIAL

Man is somewhat more than a psychosomatic scheme. He is, in addition, a social, a gregarious unit, and social influences must perforce reflect themselves in his psychosomatic equipment. The individual under discussion is, in reality, a socio-psychosomatic unit in the social order. In addition

\* Read at the Cleveland meeting of the American College of Physicians April 5, 1940.

deformity at the hip joints. If the lumbar curve is flattened there is strain of the sacroiliac and lumbosacral ligaments or abnormality or disease of the lumbar vertebrae. If there is active bone disease or fibromyositis in the lumbar region, all movements of the lumbar spine will be limited or absent.

When there is an increased inclination of the pelvis the buttocks will be prominent. This may be due to muscular weakness, to a lesion of the hip joint or to habitual faulty posture. A protuberant abdomen in a child is usually a part of a generally faulty posture, with all spinal curves increased. In an adult it may be due mostly to excessive abdominal fat, which is in itself a frequent cause of lordosis.

Viewed laterally, the knees should be straight. Recurvation is indicative of muscular weakness or paralysis, marked ligamentous relaxation or limitation of dorsal flexion of the foot at the ankle, which forces the tibia to incline downward and forward when standing with the heel on the ground. A knee held slightly flexed while standing is a weak knee. It may be due to an inflammatory condition in the joint or to a mechanical obstruction to full extension, such as internal derangement or contracture of the hamstrings.

Viewing the patient from the front, look for any enlargement about the neck and, if any is found, palpate it for heat, consistency, tenderness, movability, pulsation and motion accompanying the act of swallowing. Keep in mind adenitis, tumor and goiter. Look for any limitation of the movements of the head and neck. It may be due to spasm protecting a bony lesion, to an inflammatory condition in the soft parts or to muscular contracture. Asymmetry of the neck may be due to wry-neck, tuberculosis of the spine, abnormal vertebrae or paralysis. In congenital wry-neck rotation and lateral bending are limited by a shortened sternomastoid muscle. If of long standing there will be asymmetry in the development of the bones of the head, especially those of the face. In every case the measurements of the muscles when put in the stretch will be found to be different. Congenital wry-neck is usually noted by the mother during the early months but should not escape the observation of the physician. A wry-neck which develops during childhood is probably caused by tuberculosis of the upper cervical vertebrae. The chin will be pointed to that side on which the sternomastoid muscle is contracted, thus differentiating it from the congenital condition where the chin is pointed toward the longer muscle. In tuberculosis the neck will be immobilized, while in congenital wry-neck the head can be moved, without exciting muscular spasm, further in the direction of deformity. Enlarged glands, draining some higher infection, may cause a wry-neck in the effort to prevent pressure and pain. Congenital deformity of any of the upper cervical vertebrae may cause a wry-neck. Paralysis may be a cause. Tonic spasm of the posterior cervical muscles may be a cause, though it is rare. Clonic spasm may be a cause and is easily recognized. Hysteria must be borne in mind.



to his internal environment, which caught Claude Bernard's fancy, man exists in an external environment. *Weltanschauung* is the term used by Dunbar to designate the individual's awareness of his relationship both to the inner and outer world in terms of emotion, intellect and endeavor.

The increasing complexity, particularly of modern, urban existence, has precipitated major problems in the socio-psychosomatic realm which are disturbing the lives of increasing numbers of men, women and children. These broader problems need to be analyzed in the light of modern, scientific knowledge so that their extent and depth may be appreciated and practical methods for solutions be considered. Until recently the analytical approach to these problems has been piece-meal and generally chaotic.<sup>2</sup>

The effort to interpret the maladjusted individual in functional terms as an integrated whole reacting to other individuals within a given set of circumstances, has opened a new approach to problems of the individual as well as the community.

### SOCIAL COMPONENTS

The social components which affect man need to be analyzed by the same objective methods that are being utilized today in the study of specific disease processes. For purposes of elucidation the social components may be defined as those products of the individual and his environment that play a part in the loss of, or the failure to regain a healthy status, or those factors that may prevent him from favorably reacting to indicated therapy and/or that may hinder him from an adequate adjustment to his disability or station.

And from a different approach one needs to consider community inadequacies, the lack of certain necessary facilities in equipment, personnel and methods for the use of the same in furnishing preventive and curative medical services to those who need them. The lag which exists between current available medical knowledge and its application to problems of individual and community existence may well be regarded as a major social component of medicine at the present time.

TABLE I

Social Components in Medicine	
I.	Deprivation of physical needs
II.	Personal dissatisfactions
III.	Community inadequacies

As self-preservation is the first law of nature, there are certain irreducible essentials such as food, clothing and shelter, without which human existence cannot survive. These basic physical needs must be safeguarded for the individual to have adequate protection and be able to carry on.

A decent shelter with accommodations that are not too crowded and that furnish at least a minimum of sanitary service is an essential for a healthy status.

he can anticipate that flexion and ulnar deviation will soon be definite deformities.

Distortions can be controlled by simple methods. If the joints are so painful that even slight motion causes distress, a short period of complete immobilization of perhaps from five to seven days may provide sufficient relief to permit active and passive motion. The joints should be immobilized in the position in which the doctor finds them, and *circular* plaster of Paris casts, or one of the newer substitutes<sup>31</sup> should be used. When the plaster is applied with gentleness and care, anesthetics are not necessary. Let us consider an adducted, painful shoulder with the arm held to the side of the body. When pain has subsided sufficiently to permit motion, the arm should be abducted<sup>32</sup> gradually by placing supports between the arm and chest wall. The abducted arm can rest against these supports without the active use of the patient's own muscles. In like manner, the flexed elbow can be extended and supinated gradually. When active motion can be carried out without pain, a device such as that shown in figure 14 can be



FIG. 14. (Left) Simple apparatus increases motion and respiration.  
FIG. 15. (Right) Acutely inflamed joint completely immobilized in cast.

used to encourage active abduction. Such a method of exercising not only overcomes the tendency to fixed deformity, but also encourages muscle development and can be used as an exercise for respiration.<sup>9</sup> The use of the apparatus increases motion in all the joints of the upper extremity. It is important to see that the patient actually abducts his shoulders and not merely goes through the easier movement of forward flexion.

#### COMPLETE IMMOBILIZATION OF JOINTS

It might be well to comment on the complete immobilization of acute joints. Many doctors feel that complete immobilization results in ankylosis. This is not true.<sup>33</sup> If ankylosis takes place, it is the result of the inflammatory process causing a destruction of the articular cartilage. Im-

mobilization in circular plaster puts the inflamed joint at rest<sup>34</sup> and favors a subsidence of the inflammation, thereby actually preventing destruction of the joint. A word of caution<sup>10</sup> is necessary in the use of immobilization. Joints should not be immobilized indefinitely, but rather for periods of from five to seven days. If necessary, casts can be reapplied, but the joints should be inspected at short intervals. Figure 15 shows an acute knee which was completely immobilized for one week. At the end of three weeks, by means of active motion alone, the patient had gained full flexion of his knee joint, as seen in figure 16. Circular plaster of Paris can be used with impunity in the treatment of acute joints, provided the care is thoroughly supervised during the period of immobilization.

Another advantageous use of immobilization of joints is demonstrated in figures 17, 18 and 19. The patient, a chronic rheumatoid arthritic, had



FIG. 16. (Left) Same knee as in figure 15; three weeks later. Immobilization encourages return of function.

FIG. 17. (Right) Flexed knee due to muscle spasm of months' duration.

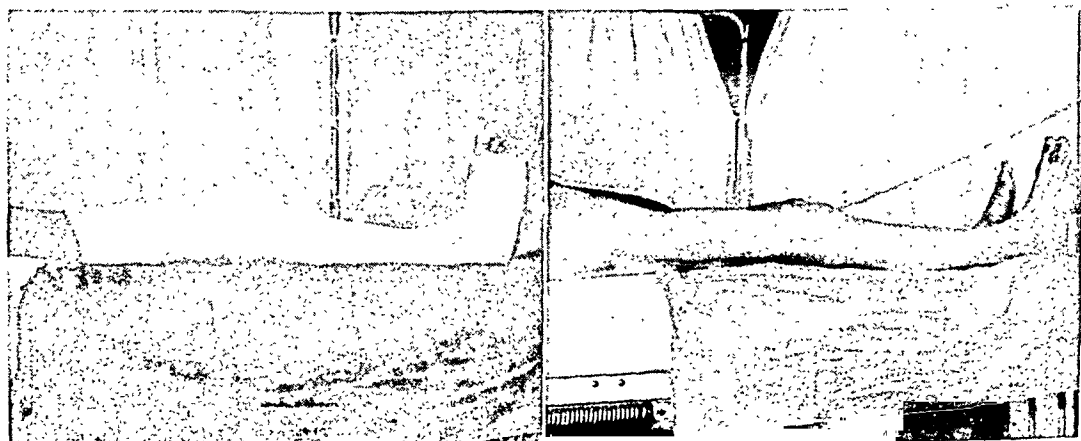


FIG. 18. (Left) Same knee as figure 17. Flexion maintained. Immobilized for rest and comfort.

FIG. 19. (Right) Four days later. Same as figures 17 and 18. Rest alone makes extension possible.

A certain minimum of quality and quantity, as well as variety of food, is essential.

An individual should have sufficient clothing to protect his body and supply a modicum of respectability.

As many experienced social workers point out, deprivation of one of these primary essentials may have more effect on one individual than on another. That is, adjustment to environmental limitations is a quality within the individual himself.

Immediately subsequent to the primary needs are the problems of education, employment and recreation. Where there is widespread lack of these necessary essentials, the combined resources of society need to be energized in the search for a solution.

### THE SOCIAL DIAGNOSIS

Social dissonances commonly reflect themselves in psychosomatic disorders. The clinical picture as seen by the attending physician is very often typical of an underlying organic lesion. In the absence of an adequate and accurate social history the most important features in the case are frequently missed entirely. The social history is of fundamental importance in the majority of patients who call upon the doctor or visit the clinic for medical advice. This is generally true of all classes of society. Whereas a great many in the lower income groups are hard-pressed by problems of deprivation of physical needs, many individuals in the upper strata of financial competence are the victims of social maladjustments that are of sufficient magnitude to produce physical illness. The dissatisfactions of life and the stresses and strains that result from high-pressure in the world of industry and the professions contributed to physical and mental breakdowns. Coronary disease is said to be ten times more frequent today than it was a generation ago.

It is within the realm of medical study and opportunity to question the patient regarding his objectives, to search for frustrations that may have played a part in his illness. The patient consults his physician for peace of mind. The diagnosis matters not to him so long as he obtains relief.

Problems of this nature are time-consuming, and because they require contacts and an investigation of social background and an analysis of the stresses and strains under which an individual is living, they are too commonly ignored by the examining physician, to the patient's detriment. It is indeed unfortunate that the doctor has not the time and, frequently, not the interest, to enter the further recesses of the patient's experience. Because of this fact the medical social worker has come upon the scene and proved herself an invaluable ally to the doctor. To her has fallen the responsibility of visiting the home, the factory, and other locales wherein the patient has made his social contacts. Information thus obtained aids the doctor in a clearer understanding of the patient and his environment and, furthermore, often



FIG. 1. Photomicrograph of section of biopsy of liver. Note intact liver parenchyma at lower right in the vicinity of the portal canal. The remaining tissue is necrotic except for small area in upper left portion of section (Courtesy of Dr. J. Felsen).

tissue, regeneration and compensatory hypertrophy of unaffected hepatic cells, with eventual hobnail fibrosis. When the repeated thromboses prove too great a burden for the collateral circulation, and the hepatic damage becomes too

uncovers information that should prove helpful in planning a convalescent régime.

Because of the important part that social components play in the causation of disease processes, a number of medical schools have utilized the experiences of professional medical-social workers in the training of medical students.

TABLE II

Medical Schools Where Social Workers Participate in the Training of Medical Students<sup>3</sup>

1. Harvard	7. Tufts
2. Johns Hopkins	8. Vanderbilt
3. Pennsylvania	9. Virginia
4. St. Louis	10. Western Reserve
5. Syracuse	11. Yale
6. Tulane	

In a stimulating book, "The Patient As A Person," G. Canby Robinson<sup>4</sup> has described the experiences which he and his colleagues at Johns Hopkins have had in the study of some 175 patients who came to that hospital for assistance. In 80 per cent of the patients studied by Robinson, some type of adverse social condition played a part in the patient's illness. The excellent results which were obtained in finding an adequate and satisfactory solution in many of the cases described by Robinson would have been impossible without the coördinated study of the entire situation, i.e., of the socio-psychosomatic pattern by the doctor in charge, assisted by the medical-social worker.

#### ADVERSE SOCIAL FACTORS

A number of individuals whose experiences have justified respect for their opinions were asked to name the most important adverse social conditions which affect people in their particular localities.<sup>5</sup> The following table is a composite of the answers received:

##### I. Deprivation of physical needs:

a. Shelter, overcrowding; food, clothing.

b. Hazardous occupations and occupational strains which predispose to diseases and undermine the general health.

##### II. Problems of financial income:

Many workers have demonstrated prompt return to health when income is made adequate to needs. However, it is frequently necessary that adjustment to insufficient income be made. Something has to be done about financial inadequacy and often the individual has to combat a community attitude. The sense of failure is a devastating thought.

##### III. Lack of education in matters of health essentials; general indifference. Attitudes of ignorance, superstition, and fear on the part of

widespread, these patients die, usually a few months after the onset of the illness, although some cases survive a number of years. The cause of death in these patients is hepatic insufficiency. It seems to us that the terminal stages often resemble the hepato-renal syndrome, as frequently encountered following operations on, or injury to, the biliary system. The increasing mental cloudiness, lethargy, vomiting, oliguria, varying degrees of non-protein retention, and icterus (although marked jaundice is rare), are indicative of the hepato-renal syndrome.<sup>18</sup>

The following case report is an example of the acute form of the syndrome.

#### CASE REPORT

*First Admission:* E. E., a 21-year-old married native Jewish female, was admitted to The Bronx Hospital private medical service of Dr. A. Goldman, in collapse, pulseless, and pale. There was a history of only a few hours' duration, initiated by vague epigastric pains, followed in close succession by repeated vomiting, rapidly increasing weakness, dizziness, and stupor. The patient had had a spontaneous incomplete abortion about three months prior to her admission, followed by bleeding, for which the uterus was curetted. There was no further menstrual irregularity, and no symptoms referable to any of the systems, nor was there any other pertinent past history. Examination revealed an obese young white female; she was pale and stuporous. Respirations were 24 per minute. There was no dyspnea or cyanosis. No pulse could be felt and the blood pressure was not obtainable. The heart sounds were slow and distant. There were no other positive physical findings.

The rectal temperature on admission was 99.4° F. The hemoglobin was 90 per cent (Sahli method; 14.5 grams equals 100 per cent). The red blood count was 4,700,000 per cu. mm.; the white blood count 15,300 with a moderate polynucleosis and shift to the left (82 granulocytes, 7 per cent of which were band forms). The specific gravity of the urine was 1.022; it contained albumin 2 plus, a few hyaline casts, and a small number of white blood cells. The benzidine test was negative, the test for bile faintly positive, and urobilinogen was present in a dilution of 1 to 40. Blood Wassermann and Kahn tests were negative. An electrocardiogram revealed no evidence of myocardial disease. There was, however, a tendency to right deviation of the electrical axis.

The patient's temperature ranged about 100° during her first week in the hospital, and was normal thereafter. After two days in stupor, she responded to stimulation, and to the administration of saline and glucose intravenously, and regained consciousness. She then began to complain of epigastric pain and nausea, and she vomited a few times. A slight icteric tint was detected in the sclerae. An attempt to obtain an adequate history from the patient at this time was unsuccessful; her responses were delayed and usually irrelevant; she resented being questioned, was lethargic and exhibited lack of interest in her attendants and family. Examination at this time revealed only a few scattered areas of abdominal tenderness, more evident on the right side. Rigidity and rebound tenderness were absent. Vaginal examination was negative. The clinical impression was that the patient had acute pancreatitis. The icterus index was now 22.7. Four repeated white blood counts gave values from 14,200 to 24,500 with neutrophilic polynuclear cells 68 to 81 per cent and band forms 5 to 12 per cent, the lower values representing those of the last count taken. No abnormal cells were seen in the peripheral blood.

The patient's condition improved gradually; she first took liquid, and then solid food well; her pulse increased in volume; her only complaint was mild right upper abdominal pain, and the only finding was persistent moderate tenderness in that area.

individuals represent an exceedingly common barrier in the maintenance of sound health. A distinguished lay authority recently stated: "As a layman, I am appalled at the ignorance of the average individual with reference to health matters." For worthless proprietary medicines, quacks, charlatans and pseudo-medical care, the nation wastes millions of dollars yearly.

IV. Maladjusted family relationships. This is one of the common bases for ill health. Social situations within families create wrong attitudes towards health which frequently produce somatic as well as psychic turmoil.

V. Unstable personalities and borderline mental deficiencies. Governmental statistics indicate that in 1936 there were 100,000 persons in institutions for mental, epileptic and defective patients. Weaver suggests that as many as five million fellow-men, more or less mentally inferior, offer serious impediments to social adjustment.

VI. Community inadequacies. Under this heading some authorities place lack of personal service for medical care; the need for convalescent homes; the necessity for hospitals in deprived areas; health centers; facilities for the rehabilitation of patients; provision for the chronically ill and mentally handicapped; a more general interest in preventive medicine and health education.

To obtain more specific information a series of 200 patients in The Lankenau Hospital was studied. The Medical Staff of the hospital was ably assisted by Sister Elba Dyer, social worker, to whom fell the responsibility of the social study in each case. One hundred and seventy-eight patients were in the hospital and 22 were clinic patients. One hundred and seventy-seven demonstrated some organic lesion; 20 were diagnosed as having functional conditions; and three were undiagnosed.

### THE SOCIAL COMPONENTS IN ILLNESS

#### *A Medical Social Review of 200 Cases in the Lankenau Hospital*

#### I. Deprivation of Physical Needs

##### A. Lack of sustenance

1. Inadequate food 2

2. Special diets for diabetic, or ulcer cases, and for drugs 24

##### B. Lack of adequate shelter 1

##### C. Lack of economic security 41

##### D. Physical strain 16

##### E. Unhealthy environment 25

##### F. Lack of personal service 19



She was discharged improved, two weeks after admission, with a final diagnosis of acute pancreatitis.

*Second Admission:* One day after the patient left the hospital, she had three loose bowel movements, followed by a seizure of acute, intermittent right lower abdominal pain, radiating over the whole abdomen. There were no associated symptoms except nausea. She was readmitted to the ward medical service. Physical examination at this time revealed the patient to be weak and drowsy; her skin was warm and dry; the body weight was 176 pounds; blood pressure was 90 mm. mercury systolic and 60 mm. diastolic. The heart and lungs were negative. There was slight ankle edema. The abdomen was markedly distended. On percussion there was dullness in the flanks, tympany over the mid-abdomen, and shifting dullness; fluid wave was definite. Abdominal tenderness was generalized, most marked over the mid-epigastrium and right hypochondrium, with moderate rebound tenderness, but no rigidity. The superficial veins of the lower chest and upper abdomen were dilated. There was a sensation of a palpable right upper quadrant and epigastric mass, the limits of which were obscured by the distention, and ascites. Her urine was normal except for the presence of a very faint trace of bile, and urobilinogen in a dilution of 1:30. Her red blood cells were 5,100,000 per cu. mm. and her hemoglobin 78 per cent. The white blood cells were 14,200 per cu. mm. with 78 per cent polymorphonuclear neutrophils, 20 per cent small lymphocytes and 2 per cent monocytes. Blood glucose was 92.6 mg. per cent and the diastase in the blood plasma normal. Her erythrocytic sedimentation rate was markedly delayed (105 minutes for 6 millimeters). Roentgenograms of the chest and abdomen showed no free subdiaphragmatic gas. The small and large bowel contained an excess of gas.

On the day of admission 500 c.c. of ascitic fluid were withdrawn by paracentesis performed in the left lower abdomen; it was clear, sterile and contained only a few erythrocytes. Abdominal fluid injected into a guinea pig did not result in tubercular lesions after six weeks. On her third hospital day, an electrocardiogram showed no cardiac abnormality. Circulation times were also normal; i.e., ether, or arm to lung time, was six seconds (normal 3.5 to 7 seconds); saccharine, or arm to tongue time, was 7.5 seconds (normal 7 to 14 seconds). Her venous pressure in the left antecubital vein was 105 millimeters of water (normal 40 to 120 millimeters); and liver pressure maintained for 30 seconds caused a very rapid rise of 55 millimeters in the venous pressure (normal a slow rise not above 40 millimeters after one minute).

Six days after admission the patient was transferred to the surgical service of Dr. William Klein. A second abdominal tap yielded 2050 c.c. of clear thin yellow fluid; air was injected and roentgenograms of the abdomen taken immediately afterwards failed to outline any masses. The air appeared under the diaphragm. After withdrawal of the fluid a smooth firm liver edge was easily palpable about one and one-half inches below the costal margin. Urinary bile was now more strongly positive, and the urobilinogen had increased so that it was detected in a dilution of 1:160.

*Operation:* On the patient's ninth hospital day an exploratory laparotomy and biopsy of the liver were performed under spinal anesthesia by Dr. William Klein. The peritoneal cavity contained several liters of serosanguinous fluid. There was no peritoneal reaction. The pelvic organs were normal. The gall-bladder was tense and did not empty with ease. Palpation of the foramen of Winslow failed to reveal a pulsation in the portal vessels. The edges of the foramen seemed to be quite rigid as though there might be fixation of the anterior wall due to thrombosis of the portal vein. Palpation of the stomach and omentum revealed no varices. The pancreas the normal size, smooth and rubbery, and its border was sharp; the liver was markedly enlarged and, like the spleen, smooth and rubbery with a sharp edge. A biopsy of

## II. Personal Dissatisfactions

## A. In the home

1. Marital friction 26
2. Parent-child friction 29
3. Living with in-laws 6
4. Conflict among other members of family as brothers, sisters, relatives, etc. 26
5. Lack of family group 19

## B. Dissatisfaction with work 7

## C. Fear of loss of social status due to illness 17

## D. Fear of dependency as result of illness 29

## E. Inability to adjust to changes in way of living or occupation 25

## F. Lack of satisfying social life.

1. Single person living alone 8
2. Lack of recreational outlets 21

## G. Personal inadequacy 75

In 57 cases no social factors were evaluated as contributing to the patient's illness or preventing his recovery. In nine of these patients social factors such as marital discord, parent-child friction and unemployment were present, but they exerted no influence on the patient's health.

TABLE III

Report on Two Hundred Patients Treated in the Lankenau Hospital  
Frequency of Adverse Social Factors

Number of patients	Number of adverse social factors
57 .....	0
37 .....	1
41 .....	2
20 .....	3
22 .....	4
13 .....	5
5 .....	6
5 .....	7
2 .....	8
2 .....	9

In approximately 100, or 50 per cent of the patients, there were one, two or three adverse social factors uncovered in the study; in 15 of the patients there were from six to 10 adverse conditions that impeded the patient's opportunity for good health.

## SOMATIC DISORDERS PRESENT IN THE SERIES OF 200 CASES

In the series of 200 patients herein presented for discussion, 104 had some organic lesion in the cardiovascular system; 51 were diabetic; 42 displayed a lesion in the gastrointestinal tract; and 38 had respiratory tract pathology; disorders of the nervous system or a definite psychosis were present in 39 patients.

the liver was taken; the cut section was tense, congested and friable and bled very little; the defect was closed with chain suture.

Pathologically, the biopsied specimen showed, on gross examination, a wrinkled, whitish, yellow capsule and marked congestion. Microscopically, there were seen multiple areas of hemorrhagic infarction, occupying approximately two-thirds of each liver lobule. The hepatic cells near the periphery of the lobules (those bordering on the portal canals), were relatively normal, while those nearer and about the central veins exhibited swelling, vacuolization, and fragmentation with widespread degeneration into necrotic hemorrhagic debris. Several of the larger hepatic vessels were thrombosed.

*Postoperative Course:* Pre- and postoperative temperatures were low grade, reaching 101°. Shortly after the operation the patient became emotionally more unstable than she had been, weeping and screaming, and very apprehensive; or often she would lie motionless and refuse to respond to questions or recognize people with whom she had shortly before been holding a somewhat rational conversation. She refused oral feedings almost entirely, and her intake was maintained by parenterally administered fluids and by gavage. In spite of repeated gastric lavage, the patient vomited daily large amounts of dark brown fluid, which gave a four plus benzidine reaction, and contained red blood cells on microscopic examination. There was a continuous serosanguinous discharge from the wound. On the fourth postoperative day, the patient lapsed into semi stupor, punctuated by screams. She became incontinent of urine, oliguric and slightly icteric. Her blood chemistry revealed a glucose level of 118.4 mg. per 100 c.c.; a non-protein nitrogen of 48.0 mg. per 100 c.c.; a uric acid of 4.3 mg. per 100 c.c.; and a creatinine of 1.18 mg. per 100 c.c. Serum bilirubin was 3.0 mg. per 100 c.c. of serum; icteric index 33 and the Van den Bergh reaction direct immediate. Blood cholesterol was 173.9 mg. per 100 c.c.; unfortunately the quantity was insufficient for cholesterol ester determination. On the seventh day the patient had a chill and a temperature of 104.7°, her pulse weakened and she died the next day in deep coma, one month after the onset of her illness.

## DISCUSSION

*Pathology:* The diagnosis of Chiari's syndrome is rarely made in life. However, at post mortem, the association of a liver showing marked atrophy from venous congestion with a normal heart immediately suggests the site of the lesion. The hepatic vein occlusion leads to back pressure atrophy of the liver, enlargement and engorgement of the spleen and marked ascites. The adventitia and muscularis of the veins are almost unaffected, with only a slight amount of fibrosis and infiltration of these coats at the ostium of the occluded vein. Stimulation to inflammatory change arises within the lumen. This represents an endophlebitis. In endophlebitis the intima may become thickened by inflammatory proliferation, independent of any deposit of thrombus upon the intimal surface (pure endophlebitis); or, the organization of thrombus by the intima may play the chief rôle (thrombophlebitis).<sup>5</sup> By constricting the hepatic vein in dogs, Simonds and Callaway<sup>14</sup> found that the large size of the liver is due to the trapping of blood in the organ; to swelling of the hepatic cells, and to edema. Following this swelling, granulation and extensive necrosis of one-half to two-thirds of the central part of the liver lobule occur, with formation of hyaline thrombi in the central and sublobular veins. As the disease progresses fibrous tissue replaces the destroyed hepatic cells. The remaining islands of hepatic cells proliferate; this results in a small hobnail organ resembling that found in Laennec's cirrhosis.

TABLE IV  
Somatic Diagnoses

Allergy .....	16
Anemia .....	9
Arthritis .....	12
Carcinoma .....	12
Cardiovascular .....	104
Diabetes .....	51
Disorders of gastrointestinal tract .....	42
Disorders of kidneys .....	6
Disorders of respiratory tract .....	38
Malnutrition .....	8
Miscellaneous .....	43
Pelvic disorders .....	26
Psychosis and disorders of nervous system .....	39
Syphilis .....	12
Thyroid .....	6
Undiagnosed .....	3

Adverse social factors are more prominently associated with chronic illnesses than with acute disorders. The longer the illness the more likely is a social problem to present itself.

Certain somatic diseases which impose future restrictions on the patient's activity as, for example, heart disease, create social problems which require long range planning to meet the patient's needs.

#### SOCIAL THERAPEUTICS

In the group of patients studied by Robinson, as well as in the present series, 75 per cent of the patients presented one or more social factors bearing on their illness. Where a deficiency of physical necessities as food or clothing existed, various social agencies were consulted and means for supplying the necessities were arranged. In addition to this, rehabilitation of the patient himself was always kept in mind. Frequently it becomes necessary to survey an entire family or larger social group and have one or more conferences with the family or group to determine practical methods of procedure. Education of the patient and/or his group is essential for any lasting improvement of status. Too frequently patients revert to their former state upon leaving the hospital, thereby nullifying efforts of doctor, nurse and social worker in their behalf. When patients demonstrate a social incapacity, a margin of support must be built up in his family or group to furnish him with the necessary steadying influence to carry on.

#### THE INCENTIVE TO RECOVERY

When an individual is motivated in the direction of certain definite objectives, the incentive to recovery is apt to be strong and that patient will more likely call upon his own resources to regain his mental poise. It is an unfortunate and common experience for doctors to find patients in wards and clinics who have no objectives, no motives and no incentive to recovery. Their lives have no direction, they are aimless, and they gravitate more and

*Differential Diagnosis:* The differential diagnosis must be made from other diseases associated with enlarged liver and ascites. The acute cases must be distinguished from myocardial failure since both result in enlarged tender liver, ascites, cyanosis and varying degrees of pulmonary congestion. Absence of marked edema of the legs, of dyspnea, and of distended cervical veins aid in the differentiation, as does the presence of normal circulation time in Chiari's syndrome.

The chronic cases must be distinguished from atrophic cirrhosis of the liver, constrictive pericarditis, tuberculous peritonitis, Banti's syndrome, and diffuse carcinomatosis of the peritoneum with ascites. In cirrhosis of the liver there may be an evident etiological factor in the form of lues, avitaminosis, or alcoholism. The liver is nodular, and has a sharp hard edge; it is not tender, in contrast to the markedly tender, smooth, round-edged liver of Chiari's syndrome; moreover, the ascites and other symptoms are gradual in onset; the patient is usually older. Tuberculous peritonitis is distinguished by the fact that the tuberculous fluid is not a transudate, by signs of peritoneal inflammation and by other evidence of tuberculous infection. Diffuse carcinomatosis with ascites should give evidence of a primary growth. Banti's syndrome is associated with anemia, leukopenia, hematemesis. Constrictive pericarditis is differentiated by the history, the engorged systemic veins, elevated venous pressure, and by roentgen-ray and fluoroscopy.

#### COMMENT

In spite of the lack of an autopsy, we believe the case here reported is an example of the acute form of Chiari's syndrome due to a primary partial thrombosis of one or both of the hepatic veins with retrograde propagated thromboses of their tributaries.

The entire course of the disease covered approximately one month. The past history contained no significant primary factor. The dilatation and curettage that preceded the onset of the disease by a few months was probably of no import, especially since the postoperative course was normal. Moreover, the pelvic veins are systemic in character, and thrombi in them could involve the hepatic veins only by retrograde thrombosis from the inferior vena cava—an unlikely occurrence, although such cases have been reported.<sup>19</sup> Other possible etiological factors were also absent, as far as could be determined. There was no evidence of syphilis, or of polycythemia, and, at operation, no evidence of carcinoma or inflammation, although the hepatic veins themselves could not, of course, be inspected at laparotomy. The diagnosis of hepatic vein thrombosis in this case was based on the following data. There was the typical history of epigastric pain, and rapidly accumulating ascites. There were, too, the findings of enlarged tender liver, dilated superficial abdominal veins, latent jaundice, and slight ankle edema. (Ankle edema has been reported in many other cases—usually proportional to the degree of involvement of the inferior vena cava in the thrombotic process.) The negative chest roentgen-rays, and normal electrocardiograms and circulation times rule out a cardiac, and probably a tuberculous basis for the symptoms; the latter is further eliminated by the fact that the ascitic fluid was negative on guinea pig inoculation. The diagnosis was con-

more to the vegetative existence. When the doctor or social worker can instill in his patient's mind a definite goal towards which to strive, a significant therapeutic measure has been created. The incentive to recovery is a necessary objective in the patient's socio-psychosomatic existence. The creation of an all-absorbing motive helps many a patient through the morass of personal dissatisfactions, the result of unhappy or unfortunate social experiences. And it was recently said by a great and noble man, that working towards a goal has its own reward, if it is only sound sleep.

### ASSETS FOR SOUND HEALTH

A study of the patient as an individual, with or without a somatic lesion, and/or an added health deficit of social origin, should bring into clear relief the assets necessary for sound health. When the patient's environment and social background are included in the study it becomes more and more evident that proper nutrition, a place to live and a reasonably well-balanced emotional equipment are essential for the maintenance of body vigor in modern society. A deficiency in one or more of these prime essentials is often the most important part of the diagnosis. Then, restoration of the patient's social balance, plus the promise of sufficient material supplies to meet his physical needs, becomes the first logical step in the adequate treatment of the patient and his rehabilitation as a social unit. The use of potions, pills and elixirs plays but a minor part in reconstruction of fellow-beings.

It is beyond the scope of this paper to discuss in detail the therapeutic methods that were used in the care and supervision of the 200 patients herein tabulated. The aim of the discussion has been to emphasize the need for a broader approach in the study of the patient as a person.

### COMMUNITY INADEQUACIES

A number of authorities have voiced the opinion that inadequate facilities for satisfactory medical care may be demonstrated in many communities throughout the country. Where deficiencies in the form of hospital service or an absence of qualified medical practitioners exist, sufficient funds should be made available for provision of the same. Medical service is so instinctively a local problem that it would appear advisable for local authorities to assume the responsibility and direction of community projects.

The most definite need today is not so much construction of more buildings, but rather an intensive and widespread educational campaign to impress upon the laity, rich and poor in all walks of life, that sound health is very largely a matter of their own responsibility. That many individuals in every community need medical care cannot be denied; that they do not receive it because of the medical profession's unwillingness to render it has never been proved. In no community of this country has there been a widespread demand for medical service that has not been met by the profession locally.

firmed by laparotomy and biopsy: the hepatomegaly and splenomegaly, the congested friable liver with pathological histology of hemorrhagic infarction surrounding the central veins, and thromboses of the larger vessels. Death, with manifestations of hepatic insufficiency, was also typical.

The venous pressure was of interest. The members of the peripheral vascular service (Dr. Saland, and associates) made the preoperative diagnosis of an obstructive lesion between the right auricle and the liver on the basis of such determination. As mentioned in the case report, venous pressure and circulation times (ether and saccharine) were normal. However, pressure over the liver for 30 seconds resulted in an immediate rise of venous pressure in the arm of 55 mm. of water (a rise from 105 to 160 mm.); the normal rise is slow and does not exceed 40 millimeters after one minute's pressure. This gave evidence of an obstruction below the right auricle (cardiac element ruled out by normal circulation time), with resultant trapping of blood in the liver. Pressure over the liver then expressed this pool of blood into the venae cavae and their tributaries, and was mirrored in the rise in venous pressure in the right anterior cubital vein. Whatever the nature of the obstruction to the hepatic veins, it must have been incomplete, else the blood could not have been expressed freely into the right auricle and superior vena cava. Had the obstruction been complete, liver pressure might then increase the venous pressure reading in the arm only by transmission of that pressure to the other abdominal viscera. This would cause a slow, gradual and slight rise, not the rapid marked rise that was obtained in this case; then again, had the obstruction been to the portal vein within or outside of the liver, and not to the hepatic veins, there would have been no liver engorgement and no marked rise in venous pressure on liver pressure. It is for this reason, the importance in differentiating ascites due to partial hepatic vein thrombosis from that due to primary portal obstruction, or due to cardiac failure, that we stress the circulation time and venous pressure readings in this case.

### CONCLUSION

A case of Chiari's syndrome, or obstruction to the hepatic veins of unknown etiology, has been presented and discussed. It is hoped that venous pressure and circulation time studies will be used in the future as an aid in diagnosing such a condition during life, and especially in differentiating this syndrome from that of portal obstruction.

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Improvement in health will become manifest as individuals develop a greater interest in their own health problems. Education of the doctor and education of the laity is, in the opinion of many competent observers, the most important health problem in the community today.

In addition to an educational campaign, the problem of facilities for the rehabilitation of patients, provision for the chronically ill and mentally handicapped, and a study of the health center idea merits more attention than has been devoted to these problems thus far.

### FINAL IMPRESSIONS

A series of 200 patients studied in The Lankenau Hospital, Philadelphia, demonstrated social factors contributing to illness in 75 per cent of the cases. A satisfactory solution to the patient's social, as well as physical problems was obtained in 90 per cent of the cases in various classes and strata. Without the sympathetic and skilled help of a professionally trained medical-social worker the medical treatment of these patients would have proved disappointing. This fact suggests a deficient study of patients when a consideration of the broader social components in disease is omitted.

The social components which affect man should be analyzed by the same objective, scientific methods that are being utilized today in the study of specific disease processes.

These social components are those products of the individual and his environment that either cause ill health or restrain the ill individual from regaining sound health.

To date, only 11 of the medical schools in the country have recognized the importance of training their students in medical social components as important factors in the causation of disease.

Every student of medicine should have a thorough foundation training in the socio-psychosomatic unit which is his patient.

A health educational program for each community is a necessary prerequisite for a healthy social order. That large sums of money are being spent on quacks, charlatans and worthless proprietary preparations is not conducive to improvement in the health of the body politic.

The medical profession and the public have an obligation and an opportunity to develop a widespread system of service that will meet the practical needs of all groups of society. With more light and less heat the wise course should be evolved without destroying any of the habits of action which have made this country the healthiest nation in the world today.

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## HEMORRHAGIC ENCEPHALOPATHY DUE TO ACETARSONE\*

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THE properties and uses of acetarsone, more commonly known as stovarsol and introduced mainly for the treatment of congenital syphilis, have recently been thoroughly reviewed by Maxwell and Glaser.<sup>1</sup> It is a pentavalent arsenic compound known as Ehrlich's 594, stovarsol in France, spirocid in Germany, and osarol in Russia. Chemically it is the acetyl derivative of 3 amino 4-hydroxy-phenyl-arsonic acid.

In addition to its use in syphilis it has been employed in various other conditions, and especially in amebic dysentery,<sup>1</sup> with apparently good results. Because of its favorable action in amebic dysentery it has been used in other types of colitis, especially ulcerative colitis and bacillary dysentery.

Acetarsone produces minor toxic symptoms as well as graver ones. Among the effects of intoxication, which necessitate the cessation of its use, are diarrhea, vomiting, fever, albuminuria, Herxheimer's reaction, purpura hemorrhagica, agranulocytosis, various forms of arsenical dermatitis, and symptoms due to

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involvement of the central nervous system. The latter symptoms range from neuritides, to paralysis, optic atrophy, convulsions, coma and death.

The purpose of this paper is to report a case of recovery from arsenical encephalopathy, which followed the use of acetarsone for bacillary dysentery, and to review the literature of so-called encephalitis following acetarsone.

#### CASE REPORT

A single female, aged 64, was first seen June 3, 1937 with a history of episodes of diarrhea since a visit to Mexico four months previously. Stools were first watery and slightly blood-tinged. Tenesmus, backache, and weight loss of seven pounds occurred in the following six weeks, and intermittent diarrhea persisted.

The past history recorded a tendency to loose bowel movements. During the past year retromanubrial and precordial pains induced by effort and relieved by rest had been noted.

Surgical history: Tonsillectomy, adenoidectomy, and appendectomy had been performed. Deep roentgen-ray therapy resulting in artificial menopause had been given in 1917 for menorrhagia.

Physical examination revealed an elderly adult female with arteriosclerotic vessels. The blood pressure was 130 mm. mercury systolic and 80 mm. diastolic. The heart was slightly enlarged; its sounds were muffled. The aortic second sound was somewhat accentuated. The abdomen was slightly tender in both lower quadrants. Neurological findings were normal.

Laboratory examinations: Blood Wassermann and Kahn tests were negative. The hemoglobin was 12.6 gm.; red blood cells 4.6 millions; white blood cells 6,250. Normal differential. Urine normal. Stools: Mucus present. The guaiac test was negative. Culture yielded a growth of *Bacillus dysenteriae dispar.* Roentgen examination with a barium meal revealed no abnormalities. On proctoscopic examination the mucosa appeared normal.

The patient was given stovarsol 0.25 gm. twice daily which she took for nine days with resulting decrease in diarrhea. On the ninth day she developed fever, nausea, and perspiration, and fainted during a bowel movement. A slight rash was noted. Temperature was 39.4° C., pulse 100, respirations 24, and blood pressure 115 mm. mercury systolic and 80 mm. diastolic.

June 21, 1937, a diffuse, blotchy, conglomerate, macular rash was seen over the entire skin surface. There was no icterus or adenopathy. Examination of blood showed: Hemoglobin 12 gm.; red blood cells 4.25 millions; white blood cells 3,500. Differential count: Polymorphonuclear neutrophiles 54 per cent; lymphocytes 44 per cent; mononuclears 2 per cent. The urine was normal. The blood chemical findings were: non-protein nitrogen, 32; sugar, 109-116 mg. per cent. Icteric index, 6. Blood chlorides, 526 mg. per cent.

The patient was placed on a high carbohydrate diet and given 5 c.c. of 10 per cent calcium thiosulphate daily.

On June 23, 1937 the patient became drowsy, nervous, tremulous, aphasic and confused. Neurological examination revealed no abnormalities. The urine was normal. White blood cells 6,250.

On June 24, 1937 there was more confusion. The tremor increased. Tendon reflexes were exaggerated. The abdominal reflexes were absent. Spinal fluid: Initial pressure, 275 mm. H<sub>2</sub>O. Cell count: Red blood cells 1,750 per cm.; white blood cells 56 per cm. Differential: Lymphocytes 94 per cent, neutrophiles 6 per cent. Test for arsenic was negative. Pandy test positive, 4 plus.

Stool culture negative. Blood: Sugar 182. Non-protein nitrogen 30, and calcium

# CASE REPORTS

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## THROMBOSIS OF THE HEPATIC VEINS—CHIARI'S SYNDROME; REPORT OF A CASE WITH BIOPSY AND VENOUS PRESSURE DETERMINATION \*

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OBSTRUCTION to the blood flow through the hepatic veins leads to a pathological-clinical entity known as Chiari's syndrome, of which there have been reported, as far as we could determine, approximately 60 cases, and which combines the clinical picture of portal obstruction and hepatic degeneration. The disease is undoubtedly often overlooked because of its similarity to the late stages of atrophic cirrhosis (Laennec's).

We are reporting a case because of its rarity, and because the clinical study included venous pressure determinations which aided in the diagnosis.

### INTRODUCTION

In 1846, Budd commented on cases of intrahepatic abscesses that involved one of the hepatic veins, with resultant thrombosis of that vein, and choking of all its tributaries even to the capillary divisions.<sup>1</sup> He quotes, as the earliest known case, one reported by Lambton in 1842.

In 1880, Schüppel suggested, in reporting a like case,<sup>2</sup> that increased blood coagulability may have been the etiological factor.

However, the disease was first adequately described by Chiari in 1899.<sup>3</sup> He reviewed the literature and brought the cases reported up to 10, including three cases of his own, in which he considered the disease syphilitic in origin. In these three cases, he found no perivascular involvement, and even very little adventitial reaction in the hepatic veins. The liver was congested, atrophic and necrotic, with secondary portal congestion and ascites. Hess, in 1905, reviewed 23 known cases and reported the first case in the American literature.<sup>4</sup> The syphilitic origin of Chiari's and of subsequent cases was questioned, and apparently disproved by Thompson and Turnbull in 1912.<sup>5</sup> In 1918 Nishikawa reviewed all the cases in the literature to date, and added 10 of his own.<sup>6</sup> In four of these, primary carcinoma of the liver supervened upon the hepatic vein thrombosis. All the known cases occurring in childhood were collected and reviewed by Hutchison and Simpson in 1930.<sup>7</sup> They added a case of their own which they had followed from the age of 5 to 28 when the patient died. At autopsy, a carcinoma of the liver was found in addition to the hepatic vein thrombosis. Since then there have been other reports of the syndrome. One case (1932) was associated with familial lipomatosis and hypertrophic osteoarthropathy.<sup>8</sup> A number of cases have been reported associated with polycythemia vera.<sup>9, 10, 11, 12, 13</sup>

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8.8 mg. per cent. Icteric index 6, CO<sub>2</sub> combining power 67 vol. per cent. Chlorides, 91 milli-equivalents, 530 mg. per cent. The patient had to be fed by duodenal tube.

On June 24, 1937 the evening temperature was 40.5° C. Intermittent tonic convulsions with opisthotonus occurred. Convulsions were more marked on right side. Spasms occurred every few minutes. Periodic respiration of the Cheyne-Stokes type was noted. Patient would stop breathing if turned on side. Sodium luminal gr. V and 0.5 c.c. of adrenalin were administered with relief from convulsions. Calcium gluconate 1 gm., 50 c.c. of 50 per cent glucose, and 200 c.c. of 5 per cent sodium chloride were given intravenously.

On June 25, 1937 the patient was comatose and had intermittent convulsions. All extremities were spastic. Bilateral Babinski responses were present. The spinal fluid contained red blood cells 5000 per cm., white blood cells 56 per cm. The exanthem was greatly decreased. Five doses of adrenalin were administered in 0.5 c.c. doses during this time. Each dose seemed to help revive patient after a convulsion.

On June 27, 1937 the patient began to react to noises. Blood examination at this time showed: Hemoglobin 11.2 gm., red blood cells 4.26 millions; white blood cells 11,700; polymorphonuclear neutrophils 73 per cent, lymphocytes 25 per cent, mononuclears 2 per cent.

June 28, 1937 the temperature was 39° C. (102.2° F.). The patient was better. Her skin was clear. Signs of cerebral edema were less. No convulsions occurred. Respirations normal. She opened her eyes and spoke. Tendon reflexes were normal. Plantar reflexes were normal. Stools and urine were passed involuntarily. Blood pressure was 90 mm. mercury systolic and 40 mm. diastolic.

June 29, 1937 the urine revealed marked glycosuria. Roentgenograms of the lungs were normal. Blood chemical findings: non-protein nitrogen 40; calcium 9.9; phosphorus 1.9 mg. per cent; serum albumin 3.1; serum globulin 3.0; total 6.1 per cent; chlorides 121 milli-equivalents, 711 mg. per cent.

June 30, 1937. Urine sugar 3+. Blood sugar 385 mg. per cent.

July 2, 1937. Urine sugar 4+. Carbohydrate diet reduced, as it became obvious that she was unable to handle the high carbohydrate diet.

July 3, 1937. Blood sugar 196 mg. per cent.

July 6, 1937. Blood sugar 152 mg. per cent. Patient lay quietly, had visual hallucinations, reacted slowly. Her speech was hesitant. Reflexes: Abdominal absent. No Babinski.

July 7, 1937. No sugar in urine. Orientation was good except for slight confusion, and loss of memory.

From here on patient gradually improved. Confusion disappeared but memory remained poor and patient had apathetic lapses. Paresthesias occurred in both arms and in the right leg which, with the exception of the left arm, cleared up in a few months.

In February 1938 the left arm was reported as extremely painful and tender on pressure. This pain ran down to the tips of the fingers and there was some heat and swelling in the left wrist and hand. At this time there was a slight wrist-drop and inability to straighten out the fingers completely. The last report received from Dr. J. G. Ely in November 1938 revealed no change for several months. Her left arm was still very painful down to the wrist, especially under the axilla and over the anterior chest wall below the left clavicle. There was considerable limitation of motion in the shoulder and in the fingers of the hand. Her general condition in other respects was very good.

#### SUMMARY OF CASE

This is a case of a woman, aged 64, receiving 4.5 gm. of acetarsone in nine days. On the ninth day fever and rash occurred, followed two days later by

Obstruction to the hepatic veins may be primary or secondary. It has been found in patients from the ages of 17 months to 70 years. The majority of cases occur in the third decade. There is no predominance of either sex. The obstruction may be intrinsic or extrinsic, and has been reported in association with a variety of lesions. Experimentally, the hepatic veins of dogs have been mechanically constricted by Simonds and Callaway in 1932<sup>14</sup> and by Simonds and Jergesen in 1935<sup>15</sup>; these men thus reproduced the pathology of the acute form of Chiari's syndrome as seen in humans. The obstruction to the hepatic veins may be produced by pressure (e.g. new growths, enlarged lymph nodes, hydatid cysts). There may be cicatricial involvement of the vein by granulomatous lesions, or other types of perivascular inflammatory tissue. When thrombosis or thrombophlebitis are found with no obvious cause, they are often attributed to infections or toxins of unknown character. Such pathogenesis is, of course, indefinite and difficult of proof. In this connection, there was a case reported by Savin in 1934 of hepatic vein thrombosis associated with iridocyclitis and exudative choroiditis.<sup>16</sup> He believed the ocular and hepatic changes had the same etiology, although he was unable to say what this was. Rigdon<sup>17</sup> believed that in the majority of cases of Chiari's syndrome there is an associated phlebitis of the hepatic portion of the inferior vena cava.

In nine cases, the syndrome has been associated with polycythemia vera. The polycythemia may be secondary to the thrombosis and portal congestion<sup>10</sup>; more often, the increased blood coagulability of polycythemia is considered the primary factor.

As mentioned above, the hepatic endophlebitis due to syphilis has not been confirmed clinically or pathologically, except when the patient has a syphilitic cirrhosis, in which case the intrahepatic cirrhotic changes precede the venous thrombosis.

The reported relationship between the chronic form of the syndrome and the subsequent primary carcinoma of the liver has also been mentioned above.<sup>6, 7</sup>

Some men have considered, but have not been able to prove, congenital malformation of the hepatic veins, such as rudimentary valves. This is suggested, usually, in cases occurring in infancy and childhood.<sup>7</sup>

The impression that the intrathoracic point of junction of the hepatic veins and the inferior vena cava is one prone to the formation of the thrombi, on a mechanical basis, likewise seems to be of little importance in view of the infrequency with which such thrombi are found at routine autopsy.

The symptoms are those of varying degrees of portal obstruction and hepatic insufficiency. The syndrome assumes one of two forms.

There is an acute type in which symptoms develop with great rapidity, and death occurs early, following a short period of vague epigastric and right upper abdominal complaints. The patient develops a congested, tender liver, a large spleen, massive ascites (the fluid reaccumulating with great rapidity in spite of frequent tapping), dilated superficial thoracic and abdominal veins, and, finally, vomiting, delirium, coma, and death from hepatic insufficiency.

In the chronic form, there are apparently repeated small thromboses, all causing incomplete occlusion, the interval between attacks allowing for the development of a collateral circulation with remissions in the signs of portal hypertension. There then follows replacement fibrosis of necrotic hepatic

coma, convulsions and opisthotonus. It appeared that she might die in any one of these spells. The administration of sodium luminal lessened her convulsions and that of the adrenalin seemed definitely life-saving. The spinal fluid showed 1750 to 5000 red blood cells per cm. and 56 white blood cells per cm. Following this recovery took place with the exception of marked pain and paresthesia in the arms and right leg, with pains and weakness still persisting in left upper extremity one and one-half years after the ingestion of the acetarsone.

#### COMMENT

So-called encephalitis following acetarsone was reviewed in the German literature by Reiter<sup>2</sup> in 1932. In this article he described the various toxic symptoms and the cerebral condition as an encephalitis hemorrhagica (*purpura cerebri*) and pointed out that it is the same type of cerebral lesion which results from salvarsan.

Three cases of encephalitis hemorrhagica appeared in the French literature following the use of treparsol.<sup>3, 4, 5</sup> The lesions and symptoms were comparable to those following acetarsone, and Reiter<sup>2</sup> reported these three cases as encephalitis hemorrhagica following acetarsone. Although acetarsone and treparsol are closely related compounds, they are not the same. Acetarsone, as already stated, is the acetyl derivative of 3-amino-4-hydroxy-phenyl-arsonic acid, whereas treparsol is the formyl derivative, both cases substituting in the amino group.<sup>6</sup>

In April 1930, Opitz<sup>7</sup> reported severe cerebral illness following the use of acetarsone in three cases of lymphogranulomatosis which resulted in two deaths due to hemorrhagic encephalitis. Aschner<sup>8</sup> reported the former two cases and added a case of Vincent's angina in which the patient received 12 tablets over a period of eight days. This patient developed a rash and convulsions, but recovered.

Reiter<sup>2</sup> added his case, that of a 36 year old male who took twenty-two 25 mg. tablets which resulted in a rash, fever, convulsions and coma, with eventual recovery except for weakness of patellar reflexes and slight stiffness of the gait five weeks later.

Since Reiter's article<sup>2</sup> no further case of definite encephalopathy following acetarsone has been reported until our present case.

Glaser<sup>9</sup> in 1934 reported two cases of arsenical myelitis and neuritides following acetarsone, and reviewed the literature on paralysis and sequelae following spinal cord involvement due to acetarsone.

#### PATHOLOGY

The pathological change in the central nervous system causing the symptoms mentioned in these cases is comparable to that produced by other organic arsenical preparations as salvarsan and treparsol.

In 1933 Globus and Ginsburg<sup>10</sup> stated that the so-called arsphenamine encephalitis was not due to inflammation but to rupture of the smaller capillaries, with moderate reactive gliosis in response to the blood and the toxic substance which had oozed through the injured vessel wall. The condition was called pericapillary encephalorrhagia.

Glaser, Immerman and Immerman<sup>11</sup> reported that hemorrhagic encephalitis

had a flexion deformity of the knee for many months. The contracture was due to a spasm of the hamstring muscles in response to the pain in the knee. The lower extremity was immobilized *maintaining* the flexion. The immobilization relieved the pain in the joint, obviating the necessity for muscle spasm. The cast was removed at the end of four days and without manipulation the knee immediately took the position of full extension. A posterior molded splint was used at rest periods to maintain the extension. When the flexion contracture is greater than shown in this case it might be necessary to use repeated casts, obtaining a little more extension with each cast until full correction is obtained. The advantages of this treatment are that it does not cause pain or the muscle pull from traction, and it saves the patient from manipulation or open operation. Primarily, this procedure avoids any damage to the joint structures.

#### AFTER CARE

If the above procedures are followed, much can be done to prevent the crippling sequelae<sup>35</sup> of chronic arthritis. However, treatment must be continued until the patient can be considered completely recovered and back to normal life.

For the patient who has recovered from the acute stage of arthritis, one must think of preparing his muscles<sup>36</sup> to do the added work required by weight-bearing when he becomes ambulatory. Massage of the back and of the muscles above and below<sup>37</sup> the joints is of primary importance in the development of muscle tissue and muscle tone. Massage should at first be very gentle and should be controlled by the patient's reaction of pain and fatigue. The massage should be given by a well-trained technician under the direct supervision<sup>32</sup> of the attending doctor. Active motion,<sup>38, 39</sup> either under water<sup>40, 41</sup> or with the patient in bed, has the double benefit of increasing mobility and muscle development. Passive motion is a form of manipulation and should be used only in special cases. When the patient first starts to walk, it is essential that he have proper footwear to maintain the correct alignment of his lower extremities<sup>35</sup> as well as an adequate brace to control any joint that is not yet capable of self-support. If a brace is required for the back, it must be at least long enough to control the pelvis and the lumbar and low dorsal spine.

When the patient is beginning to bear weight, there is a great tendency for body distortions to develop and he will have to be carefully guarded to see that at this stage<sup>18</sup> a deformity of one or more joints does not develop. Any indication of impending deformity should be given immediate attention and treated as in the acute stage of the disease.

#### CONCLUSIONS

The average deformity in the average arthritic can be prevented by the institution of orthopedic management in the early stage of the disease. Co-



operation between the internist and the orthopedist, who are primarily responsible for the care of these patients, is needed to insure concurrent orthopedic and medical care from the time the diagnosis is made.

Orthopedic management is based upon a thorough understanding of the nature and development of deformities in chronic arthritis. It requires a knowledge of basic orthopedic principles.

In this paper the orthopedic care required to prevent the development of deformity in each joint has been discussed. The correction of mild distortion has been outlined. The observation of the patient over a long period, particularly when he becomes ambulatory, is emphasized. If the principles of treatment that have been presented are followed, the great majority of patients suffering from arthritis will be spared the misfortune of the development of disabling deformities.

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was first described by Rosenfeld in 1903, and their paper reviewed cases of so-called encephalitis and myelitis produced by intravenous arsphenamine. They claimed that myelitis or myelopathy without brain involvement was extremely rare.

Russell<sup>12</sup> in 1937 believed that the symptoms in the central nervous system following arsphenamine medication could be either hemorrhagic or non-hemorrhagic perivascular lesions depending on the severity of the toxin. It appeared to him that the arsenic itself as a toxic agent was unlikely to be responsible for the lesion, because chemical analysis showed that the arsenic content of the brain in cases of arsphenamine encephalitis was lower than in those cases where death was due to poisoning with inorganic arsenic (Osterberg and Kernhan—1934).<sup>13</sup> Moreover, hemorrhagic encephalitis is not a recognized complication of poisoning with inorganic arsenic. The condition found in arsphenamine encephalitis is similar to the hemorrhagic encephalitis described by Baker,<sup>14</sup> who observed perivascular hemorrhages of a varying size occurring mainly in the white matter. He held that this condition can be caused by various infectious conditions (as measles, scarlet fever, dysentery, etc.) and that it is not a true encephalitis.

The pathological findings in Opitz's case of encephalopathy following acetarsone ranged from cerebral edema to many hemorrhagic areas, especially in the white matter of the cerebral hemispheres. These lesions are similar to those reported after salvarsan and treparsol.

Of the five cases of encephalitis following acetarsone reported in the literature, two died and three recovered. Our case recovered, giving a total of four recoveries.

From the discussion of the pathology the salient point appears to be that a true encephalitis does not follow acetarsone intoxication but that the lesion in the central nervous system is comparable to that produced by salvarsan and other organic arsenicals. The lesion seems to consist of edema and perivascular hemorrhages of varying size. The pathological changes occur mainly in the white matter of the brain but may also occur in the spinal cord. Very little or no arsenic has been found in the central nervous system in those cases in which analyses were made. In our case no arsenic was present in the spinal fluid, and this fits in with the general consensus of findings regarding organic arsenical intoxication.

From this study it is learned that dangerous central nervous system lesions can result from the use of acetarsone. It appears inadvisable to use this substance indiscriminately, especially when other more efficacious and less dangerous drugs are available.

#### SUMMARY

A case of encephalopathy with recovery following the use of acetarsone is reported and the literature concerning similar cases is reviewed.

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Dr. Samuel Cohen (Associate), Jersey City, N. J., discussed "Some Aspects of Lympho-Hematogenous Tuberculosis" at a clinical session of the Tuberculosis Sanatorium Conference of Metropolitan New York on Chronic Pulmonary Diseases, October 9, 1940. Dr. Grant Thorburn, F.A.C.P., New York, N. Y., presided at this session.

Dr. Grafton Tyler Brown, F.A.C.P., Washington, D. C., was guest speaker at a dinner meeting of the Allegany-Garrett Counties Medical Society held in Cumberland, Md., October 25, 1940. His subject was "Hay Fever"; the talk was illustrated with lantern slides.

Dr. Isidore W. Held, F.A.C.P., New York, N. Y., and Dr. Hyman I. Goldstein (Associate), Camden, N. J., discussed "Peptic Ulcer—Etiology and Management" at a meeting of the New York Chapter of the National Gastroenterological Association, held in New York City on October 21, 1940.

At a recent Postgraduate Assembly of the Montour County Medical Society Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass., spoke on "The Renaissance of Diabetic Treatment." Dr. Belford C. Blaine (Associate), Pottsville, Pa., opened the discussion on this subject.

The Los Angeles Heart Association held its 8th annual symposium on heart disease October 31 to November 1, 1940. Among the speakers at this meeting were:

Dr. James F. Anderson (Associate), Los Angeles, Calif.—"The Electrocardiographic Diagnosis of the Arrhythmias";

Dr. George H. Houck, F.A.C.P., Los Angeles, Calif.—"The Lag Screen Electrocardiograph";

Dr. Robert W. Langley, F.A.C.P., Los Angeles, Calif.—"The Clinical Uses and Limitations of the Electrocardiogram";

Dr. Archie Marvin Roberts (Associate), Los Angeles, Calif.—"Extra-cardiac Causes of Heart Pain";

Dr. Horace B. Cates (Associate), Los Angeles, Calif.—"The Heart in Disturbances of the Thyroid";

Dr. Morris H. Nathanson, F.A.C.P., Los Angeles, Calif.—"Recent Developments in the Treatment of Sub-Acute Bacterial Endocarditis";

Dr. Philip Corr, F.A.C.P., Riverside, Calif.—"Dyspnea."

Dr. E. Richmond Ware, F.A.C.P., Los Angeles, and Dr. Alvin G. Foord, F.A.C.P., Pasadena, conducted a clinical pathological conference.

Dr. Howard F. West, F.A.C.P., Los Angeles, presided at a round table discussion of questions submitted by members. Among the others who participated in this round table discussion were: Drs. Donald J. Frick, F.A.C.P., Stanley Granger, F.A.C.P., R. Manning Clarke, F.A.C.P., Solomon Strouse, F.A.C.P., and George H. Houck, F.A.C.P., all of Los Angeles.

Dr. George H. Houck, F.A.C.P., is president of this Association, Dr. John Martin Askey, F.A.C.P., is vice-president, and Dr. Louis E. Martin (Associate) is secretary.

The New York Academy of Medicine has announced that the following speakers will participate in the 15th series of Friday Afternoon Lectures:

Dr. Norman Plummer (Associate), Associate Attending Physician, Bellevue Hospital—"The Specific Treatment of Pneumonia," January 3, 1941;

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Dr. Kenneth R. McAlpin, F.A.C.P., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University—"Blood Diseases from the Standpoint of the Clinician," January 24, 1941;

Dr. W. Laurence Whittemore, F.A.C.P., Attending Physician, City Hospital—"Newer Drugs," February 7, 1941;

Dr. George M. Lewis, F.A.C.P., Assistant Physician, New York Hospital—"New Concepts Regarding Skin Infections, Especially Fungous Infections," March 14, 1941;

Dr. Cornelius P. Rhoads, F.A.C.P., Director of Memorial Hospital—"Recent Studies in the Production of Cancer by Chemical Compounds," March 21, 1941;

The following lectures have already been held:

Dr. Harold J. Stewart, F.A.C.P., Associate Professor of Medicine, Cornell University Medical College—"Digitalis Therapy: Mechanism of Its Action in Congestive Heart Failure," November 1, 1940;

Dr. Irving S. Wright, F.A.C.P., Professor of Clinical Medicine, New York Post-Graduate Medical School, Columbia University—"Thrombophlebitis—Recent Advances in Knowledge and Treatment," November 29, 1940;

Dr. Ralph H. Boots, F.A.C.P., Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University—"Gold Therapy in Rheumatoid Arthritis," December 6, 1940.

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The annual Travel Meeting of the Texas Club of Internists was held in Boston, Mass., October 21–25, 1940. Splendid scientific programs were presented for the Club at the Robert Dawson Evans Memorial of the Massachusetts Memorial Hospital under the guidance of Dr. Chester Keefer, F.A.C.P., and at the Thorndike Memorial of the Boston City Hospital under Dr. George R. Minot, F.A.C.P., and Dr. William B. Castle, F.A.C.P., on October 21; at the Peter Bent Brigham Hospital under Dr. Soma Weiss, F.A.C.P., October 22; at the Deaconess Hospital under Dr. Frank Lahey and Dr. Lewis Hurxthal, F.A.C.P., October 23; at the Massachusetts General Hospital under Dr. James H. Means, F.A.C.P., October 24; and at the Deaconess Hospital and the George F. Baker Clinic under Dr. Elliott P. Joslin, F.A.C.P., and Dr. Howard Root, F.A.C.P., October 25, 1940.

Among the Texas members of the College who attended this Meeting were: Dr. William B. Adamson, F.A.C.P., of Abilene; Drs. David Carter, F.A.C.P., Robert M. Barton, F.A.C.P., William H. Potts, F.A.C.P., Samuel A. Shelburne, F.A.C.P., J. Shirley Sweeney, F.A.C.P., and Merritt B. Whitten (Associate), all of Dallas; Drs. W. Shelton Barcus (Associate) and William L. Howell (Associate), both of Fort Worth; Drs. George Herrmann, F.A.C.P., William L. Marr, F.A.C.P., and Charles T. Stone, F.A.C.P., all of Galveston; Drs. Frederick Lummis, F.A.C.P., and LeRoy B. Duggan, F.A.C.P., both of Houston; Drs. Joseph Kopecky, F.A.C.P., Julian Barton, F.A.C.P., Edgar M. McPeak, F.A.C.P., and David R. Sacks, F.A.C.P., all of San Antonio; and Dr. Walter B. Whiting, F.A.C.P., of Wichita Falls.

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The 91st annual session of the Indiana State Medical Association was held at French Lick, Ind., October 29–31, 1940. Among the guest speakers were:

Dr. Roy Wesley Scott, F.A.C.P., Cleveland, Ohio—"Clinical Aspects of Arteriosclerosis";

Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, Ohio—"Diagnosis and Treatment of Acute Nephritis";

Dr. Charles A. Flood (Associate), New York, N. Y.—"Prognosis and Treatment in Peptic Ulcer."

## EDITORIAL

### THE SIGNIFICANCE OF CLINICAL RESEARCH \*

CLINICAL research may be said to represent the reconnaissance or intelligence arm of the medical profession. It is the most arduous, most hazardous (to reputation, if not to life), the slowest and most uncertain as to reward, and the most exacting of all scientific disciplines, bar none. It demands the highest integrity of its devotees, implying exact observation accurately reported. It involves an appreciation of the fact that any immediate interpretation of any isolated phenomenon is likely to be in error; and furthermore, that the facts so carefully and laboriously gathered and meticulously analyzed often serve others better as stepping stones to different and more important conclusions than the original investigator ever realized, or will ever admit. Devotion to Research will inevitably lead at times to the personal disappointment and chagrin attendant upon the coincident discovery, but prior presentation by others, of new data yet in the chrysalis stage in one's own laboratory or clinic: disappointment?—yes!—unless you are one of those fortunate human beings born with that happy capacity for genuine, unadulterated love of Verity for Verity's sake; unless you have been endowed with that enviable faculty of automatically sublimating all personal ambition for aggrandizement and acclaim in the mere joy of scientific achievement. Every new horizon glimpsed through some new fragmentary bit of knowledge, at once challenges the restless, adventurous, inquisitive spirit of the true investigator to a fresh, more intensive, exploration of these rapidly expanding frontiers of the mind, leaving no time for self pity or envy. In short, we who profess a research interest in medicine should possess the dominating motivation and capacity for the abstract satisfaction of those men of science, whom Claude Bernard designated as the Truth Seekers: "Ardent desire for knowledge, and this knowledge really grasped, and yet always flying before them, becomes at once their sole torment and sole happiness. Those who do not know the torment of the unknown cannot have the joy of discovery, which is certainly the liveliest that the mind of man can ever feel. But, by a whim of Nature the joy of discovery, so sought and hoped for, vanishes as soon as found. It is but a flash, whose gleam discovers for us fresh horizons toward which our insatiate curiosity repairs with still more ardor. Thus, even in science itself, the known loses its attraction, while the unknown is always full of charm." Or as Pascal put it: "We are in search never of *things* but of the *search for things*."

Being a scientific investigator, then, is a state of mind. When applied to medicine it implies an analytical approach to every problem, be it in the laboratory or clinic—an abstraction or a diagnosis. It is based upon a lively

\* From the Presidential Address to the Central Society for Clinical Research, Chicago, Ill., November 4, 1940.

Dr. Hugh R. Butt (Associate), Rochester, Minn., recently addressed a meeting of the Cerro Gordo (Iowa) County Medical Society held in Mason City, Iowa. Dr. Butt spoke on "Recent Advances in Vitamin Therapy."

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Among the speakers at the New England Postgraduate Assembly, sponsored by the state medical societies of Massachusetts, New Hampshire, Rhode Island, Maine and Vermont, November 13-14, 1940, at Harvard University, Cambridge, Mass., were:

Dr. Robert F. Loeb, F.A.C.P., New York, N. Y.—"The Practitioner and the Problems of Diabetes";

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio—"Factors in the Production of Anemia";

Dr. T. Grier Miller, F.A.C.P., Philadelphia, Pa.—"The Causes of Indigestion and Their Recognition."

Dr. Reginald Fitz, F.A.C.P., Boston, Mass., acted as toastmaster at the dinner held November 13.

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The Long Island College of Medicine, New York, N. Y., has announced that Dr. Abraham M. Rabiner (Associate), Brooklyn, N. Y., has been appointed Clinical Professor of Neurology and Psychiatry and Dr. Elliston Farrell (Associate), Brooklyn, N. Y., has been appointed Assistant Clinical Professor of Medicine.

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Western Reserve University School of Medicine, Cleveland, Ohio, has announced that Dr. John A. Toomey, F.A.C.P., has been appointed Professor of Clinical Pediatrics and Contagious Diseases, and Dr. Robert M. Stecher, F.A.C.P., has been appointed Assistant Clinical Professor of Medicine.

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Dr. Benjamin W. Black, F.A.C.P., Oakland, Calif., President of the American Hospital Association, delivered on September 23 the principal address at the 75th anniversary of the founding of the Jewish Hospital, Philadelphia, Pa. Dr. Black discussed the hospital's position in civilization.

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Dr. Joseph McFarland, F.A.C.P., Philadelphia, Pa., Emeritus Professor of Pathology and Bacteriology at the University of Pennsylvania School of Medicine, was recently appointed Professor of General Pathology at the School of Dentistry of Temple University.

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Dr. Conley H. Sanford, F.A.C.P., Memphis, Tenn., spoke on "Management of the Aged Patient" at a recent meeting of the Mississippi County (Ark.) Medical Society.

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The Southern California Medical Association held its 103rd semi-annual meeting at San Bernardino, November 15-16, 1940. Among the speakers were:

Dr. Milo K. Tedstrom, F.A.C.P., Santa Ana, Calif.—"Postural Hypotension; Report of Two Cases";

Dr. Thomas Addis, F.A.C.P., San Francisco, Calif.—"Treatment of Nephritis."

interest in and appreciation of the medical art of the past; it thrives upon an intelligent knowledge of the best current medical thought and scientific practice; but, most of all, it depends upon a sincere belief in and a consistent contribution to the better understanding and control of fundamental biologic phenomena, as they relate to health and disease.

Inherent in the personality of every physician worthy of the name is intellectual courage, and a high standard of duty to his science, to his patients, and to his community. To be sure, the greater the creative imagination combined with an actively inquiring, intelligent mind, the closer we come to human genius. But historically, more often than not, due to associated eccentricities, genius has fallen short of its promise, and to the persistent and versatile, if less brilliant, investigator goes the solution of many a perplexing problem. The most successful ways of acquiring, of using and of advancing knowledge are entirely personal and essentially elastic. *Going actually through the mechanics of performing a research, is the only sure way of becoming aware of how and why knowledge grows.*

We honor the physician, who, wherever he finds himself, and under whatever circumstances, approaches and completes each day's work with an open, alert, inquiring, analytical, expectant mind. Whether a manuscript, to stimulate and guide his peers, results or not, such a physician has earned, and deserves to be distinguished by, the honorable annotation of "clinical investigator."

Time was when a philosopher might compass within his sphere of knowledge all that was currently known of the world about him. Then the pendulum began slowly to swing toward the opposite extreme with the development of an infinite number and variety of special fields of science each further subdivided by a multitudinous minutiae of technical detail. The result was an individual limitation and jealousy of territorial rights and privileges, which greatly curtailed the interpretation and rapid resynthesis of individual facts. And such synthesis must always follow analysis, if genuine progress is to be made. This particular stage in the evolution of learning probably reached its greatest expression early in this century. Since then, however, the pendulum has started back in its swing, and we in scientific medicine today realize again with all scientifically minded men, that there is only one natural world, and there is only one knowledge of it. There is no longer one science of physics, one of chemistry, and another of mathematics, apart from biology and medicine. One contributes to all, and all contribute to even the least one of the component parts.

This places a particular responsibility and obligation upon those of us in educational and institutional positions where we are entrusted with the training, advising and directing of medical students and of the interne and resident staff men in our hospitals. If one believes in the selective service versus the volunteer method for meeting our tactical national defense needs, one will at once agree upon the desirability of, and opportunity for, the selection of young physicians with special natural endowments and capacities



Dr. Robert S. Berghoff, F.A.C.P., Chicago, Ill., was recently awarded honorary membership in Alpha Omega Alpha at his alma mater, St. Louis University School of Medicine, St. Louis, Mo.

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Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill., who, upon his retirement October 1, completed thirty-six years of active service on the faculty of the Division of Biological Sciences, University of Chicago, has donated his scientific library to the University. The collection includes nearly 16,000 classified reprints of scientific articles, 1,200 books and research monographs, and complete files of fifteen journals.

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Dr. Cornelius P. Rhoads, F.A.C.P., New York, N. Y., addressed a joint meeting of the Institute of Medicine of Chicago and the Chicago Society of Internal Medicine on "Physiological Aspects of Vitamin Deficiency," October 28, 1940.

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Dr. Thomas B. Magath, F.A.C.P., Rochester, Minn., has been elected Vice-President of the Minnesota State Board of Health.

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Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill., gave a lecture on "Age Criteria in the Pathology of Tuberculosis" at the Mayo Clinic in Rochester, October 1, 1940.

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Dr. Irving S. Wright, F.A.C.P., New York, N. Y., has been made Executive Officer of the Department of Medicine of the New York Post-Graduate Medical School and Hospital. Dr. Wright succeeds Dr. Walter G. Lough, F.A.C.P., who has been made Clinical Professor of Medicine at this institution.

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Dr. D. Sergeant Pepper (Associate), Philadelphia, Pa., was one of the guest speakers at the annual meeting of the 9th District Medical Society of North Carolina held at Mooresville, September 26, 1940. Dr. Pepper spoke on "The Use of Sulfapyridine and Sulfathiazole in the Treatment of Pneumonia."

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Dr. Harrison F. Flippin (Associate), Philadelphia, Pa., was one of the guest speakers at the 7th annual Postgraduate Day of the University of Toledo, November 1, 1940. Dr. Flippin spoke on the following topics:

"Pharmacology, Method of Administration and Toxicity of Sulfonamides";

"Chemotherapy in Special Medical Infections (Urinary Tract, Scarlet Fever, Rheumatic Fever, Endocarditis, Malaria)";

"Chemotherapy of Respiratory Disease."

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The Texas Public Health Association held its annual meeting in Fort Worth September 30 to October 2, 1940, under the presidency of Dr. George A. Gray, F.A.C.P., Sweetwater. Dr. Frederick R. Lummis, F.A.C.P., Houston, spoke on "The Present Public Health Status of Heart Disease" at this meeting.

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The friends of the late Dr. Lawrason Brown, F.A.C.P., who was for many years head of the Trudeau Sanatorium, Saranac Lake, N. Y., have established the Lawrason Brown Memorial Fund to finance one or more fellowships for research in diseases of the chest. This fund will be managed by the Saranac Lake Society for the Control of Tuberculosis. Among the members of the present committee appointed by the Society

for creative research. In medical research, as, for example, in aviation, sincerity of purpose and nobleness of ideal are no substitute for, nor assurance of, fitness for the job.

History has repeatedly attested to the increased effectiveness of the combined efforts of like-minded individuals in the accomplishing of their common objectives. Voluntary associations of those with similar interests in clinical research have a large part to play not only in stimulating investigative work but in bringing about the better teaching and the more intelligent practice of medicine.

CHARLES A. DOAN

are Dr. Louis Hamman, F.A.C.P., Baltimore, Md., and Dr. William P. Thompson (Associate), New York, N. Y.

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Recently Dr. Edgar Mayer, F.A.C.P., New York, N. Y., delivered one of the William S. Friedman Lectures under the auspices of the National Jewish Hospital, in coöperation with the Medical Society of the City and County of Denver and the University of Colorado School of Medicine. Dr. Mayer spoke on "Recent Advances in the Clinical Interpretation and Management of Pulmonary Tuberculosis" and "Pulmonary Tuberculosis in the Present Epidemiologic Phase."

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Among the speakers at a postgraduate course sponsored by the Illinois State Medical Society in Mattoon, Ill., November 7, 1940, were:

Dr. Italo F. Volini, F.A.C.P., Chicago, Ill.—"Sulfanilamide and Allied Drugs; Indications, Contraindications, Dosage";

Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill.—"Obesity, Types and Management."

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., was one of the speakers at a symposium on the gall-bladder and liver at another postgraduate course sponsored by this Society in Bloomington, Ill., October 31, 1940.

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Dr. John A. Kolmer, F.A.C.P., Philadelphia, Pa., addressed the Chicago Medical Society November 6 on "The Present Status of Chemotherapy."

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Dr. John W. Ferree (Associate), Indianapolis, Ind., has been appointed Director of Public Health of Indiana. Since 1936 Dr. Ferree had been Chief of the Bureau of Local Health Administration of the State Department of Public Health.

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The annual meeting of the Fourth District Branch of the Medical Society of the State of New York was held in Schenectady October 1-2, 1940. Among the speakers were:

Dr. Abraham H. Aaron, F.A.C.P., Buffalo, N. Y.—"Proprietary Medicine";

Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y.—"Medical Care of the Indigent Sick."

The Eighth District Branch of the Medical Society of the State of New York held its annual meeting in Niagara Falls, October 3, 1940. Among the speakers were:

Dr. N. Stanley Lincoln, F.A.C.P., Mount Morris, N. Y.—"Diagnosis and Management of Early Pulmonary Tuberculosis";

Dr. Julius H. Hess, F.A.C.P., Chicago, Ill.—"Problems in the Care of the Premature Infant."

Dr. Abraham H. Aaron, F.A.C.P., Buffalo, N. Y., was the leader of a round table discussion on therapy.

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The ninth annual Postgraduate Day of the Summit County (Ohio) Medical Society was held in Akron, October 23, 1940. Among the speakers were:

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.—"The Menace of Obesity" and "The Diagnosis and Treatment of the So-Called Secondary Anemias";

Dr. John M. Sheldon (Associate), Ann Arbor, Mich.—"Evaluation of Modern Drugs in Management of Allergic Patients" and "Diagnosis and Management of Eczema Patients."

## BOOK REVIEWS

*The Diagnosis and Treatment of Diseases of the Peripheral Arteries.* By SAUL S. SAMUELS, A.M., M.D. Second Edition. 372 pages; 22.5 × 14.5 cm. Oxford University Press, London, New York, Toronto. 1940. Price, \$6.50.

The author, in his second edition of this book, has retained the valuable conciseness of the first edition. This is an excellent monograph, on peripheral vascular diseases, that should be of value to both the clinician and the general practitioner.

Discussion is limited to the practical aspects of etiological factors and to therapy. No attempt is made to discuss pathological changes, or to obscure practical aspects by theorizing. The author's methods of therapy are demonstrated by a liberal interspersing of case records.

Chemotherapy is discussed, and valuable suggestions are given for the treatment of infections. In addition, the author describes his method of performing an amputation.

The two most common organic vascular diseases, e.g., thrombo-angiitis obliterans, and arteriosclerosis obliterans, are discussed at considerable length.

In addition to retaining chapters on Raynaud's disease, erythromelalgia and essential thrombophilia, brief discussions of the more unusual vascular disturbances have been added. These subjects are acrocyanosis; periarteritis nodosa; embolism; cervical rib and scalenus anticus syndrome; thrombosis of axillary vein; frostbite; ergotism; glomus tumor and aneurysm of peripheral vessels. The discussion of each of these subjects is brief and concise.

The chapter on the medico-legal aspects of vascular disease has been retained.

The book is liberally illustrated, and it contains both an author and a subject index.

G. H. Y.

*Clinical Roentgenology of the Alimentary Tract.* By JACOB BUCKSTEIN, M.D. 652 pages; 25.5 × 17 cm. W. B. Saunders Co., Philadelphia. 1940. Price, \$10.00.

Dr. Buckstein, in the preface to his volume, "Clinical Roentgenology of the Alimentary Tract," states that he has tried to keep in mind the points of view of both the general practitioner and the specialist in gastroenterology. To the reviewer, he has done this remarkably well, and especially has he been able to combine clinical gastroenterology with the roentgen-ray interpretation of this specialty for the physician in general practice.

The subject is presented in an orderly fashion. The various sections are devoted to particular parts of the gastrointestinal tract, each chapter beginning with a description of the normal roentgenologic appearance. The discussions of the pathological and functional disturbances are presented very adequately, the author combining his own views and those compiled from the literature in an extremely effective manner. One of the most interesting features of the book is the presentation of case histories at the conclusion of the various sections. Here are illustrated representative roentgenograms of the various disorders described, this method permitting a close correlation between the clinical and the roentgen-ray aspects of the various disease processes.

The author's style of writing is conducive to ease in reading. At no time does the reader feel that there are any concentrated scientific descriptions, but he is aware of the completeness of all the discussions. The format of the book is excellent; the illustrations are quite distinct; and the type clearly readable.

For one interested in the roentgenology of the gastrointestinal tract, this volume is well recommended.

F. G. D.

Dr. John E. Gordon, F.A.C.P., Professor of Preventive Medicine and Epidemiology, Harvard Medical School, Boston, Mass., has been promoted to Charles Wilder Professor of Preventive Medicine and Epidemiology.

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Dr. Luis M. Morales, F.A.C.P., San Juan, P. R., has been appointed a member of the Advisory Pardon and Parole Board of Puerto Rico.

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Dr. H. I. Spector, F.A.C.P., St. Louis, Mo., addressed the St. Louis Medical Society, November 26, 1940, on the subject "Some Striking Trends in Tuberculosis, Pneumonia, and Cancer of the Lungs."

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### OBITUARIES

#### DR. WILLIAM SHREVE COLLIER

Dr. William Shreve Collier, M.D., F.A.C.P., died on September 27, 1940, at his home in Trenton, N. J., after a long illness due to a carcinoma of the rectum.

Dr. Collier was just 63 years of age on the day of his death, having been born September 27, 1877. His early education was obtained at Peddie Institute; he then entered the Medical School of the University of Pennsylvania, where he was a member of Phi Sigma Kappa. After graduation in 1902, he interned for two years at the Williamsport (Pa.) Hospital.

In 1904 he took up the practice of medicine in Trenton, where he soon established himself both with patients and among his fellow practitioners, by whom he was affectionately known as "Bill." He was soon regarded as one of Trenton's outstanding physicians. He was a Fellow of the American Medical Association, took an active interest in both his county and state societies, and in 1930 was elected to Fellowship in the American College of Physicians. From early years Dr. Collier served on the medical staff of St. Francis Hospital, and was made a Consulting Physician in 1929, and Chief of the Medical Service. He was president of the Medical Board at the time of his death.

While at the University of Pennsylvania Dr. Collier played baseball, and his reputation still lingers as one of their great players. He was an ardent hunter and fisherman, and indulged himself in long holidays pursuing these sports. He was a highly respected member of the Community, a Mason and member of the Shrine. His business interests and ability were recognized by his election to directorship in two Trenton banks.

Altogether Dr. Collier's life was well rounded and useful, one of steady service to his community, which recognized his worth and mourns him with grateful memory.

Dr. Collier never married. A sister and three brothers survive him.

GEORGE H. LATHROPE, M.D., F.A.C.P.

Governor for New Jersey

*Functional Disorders of the Foot.* By FRANK D. DICKSON, M.D., and REX L. DIVELEY, M.D. 305 pages;  $23.5 \times 16$  cm. J. B. Lippincott Co., Philadelphia. 1940. Price, \$5.00.

The subject of foot disorders cannot be given the time it deserves in many schools with crowded curricula in the third and fourth years. To study the minor and major foot ailments later necessitates either an advanced course in orthopedic surgery or an extensive review of the literature which is both voluminous and confusing.

Foot complaints make up a large proportion of human ills. Some are due to minor local causes and others are a symptom of a major constitutional illness. Too often physicians pass over minor foot complaints leaving the patient no recourse but that of consulting irregular "specialists" for relief.

This book discusses in a clear, concise and orderly manner the common disorders of the foot, not only those of local origin but also those which arise as a result of a constitutional disease. The consideration of the evolution and of the mechanics of the foot is particularly well done. A very rational concept of the problems involved is clearly presented. The monograph will be of value to the internist as well as to the orthopedic surgeon.

H. F. U.

*The Hospital Care of Neurosurgical Patients.* By WALLACE B. HAMBY, M.D., F.A.C.S., xi plus 118 pages, with 24 drawings;  $22.5 \times 14.5$  cm. The Charles C. Thomas Company, Springfield, Illinois, and Baltimore, Maryland. 1940. Price, \$2.00.

This small volume will be found of interest and help to those who have neurosurgical patients under their care. There are short chapters which deal with history taking and elementary anatomy which are of value primarily to the nurse. Diagnostic procedures, such as lumbar and cisternal punctures, the Queckenstedt test, and encephalography, are briefly but adequately discussed. Discussion of the care of the bladder and the description of continuous tidal drainage will be found helpful. Other minor surgical procedures, such as venipuncture, surgical exposure of veins, blood transfusion, and administration of hypertonic solutions, are discussed. The pre- and post-operative treatment of the more common neurosurgical diseases is a very helpful guide to house officers who are just beginning their neurosurgical experience. A chapter on post-operative dressings is included.

The book is well indexed. This is the first manual of its kind to come to the reviewer's attention and will be of interest to nurses, house staff, and to general surgeons who have occasional contact with neurosurgical problems.

J. G. A., JR.

*Principles of Hematology.* By RUSSELL L. HADEN, M.A., M.D. Second Edition. 362 pages;  $15.5 \times 24$  cm. Lea and Febiger, Philadelphia. 1940. Price, \$4.50.

The second edition of Dr. Haden's book will no doubt appeal to a wide audience of medical students, clinical pathologists and internists. The method employed by the author is to present his material in concise and simplified form. He utilizes charts, figures and diagrams freely to enable the reader to visualize the data. Stress is laid on quantitative relationships, and what might be called the mathematics of the blood cells is dealt with at some length. There is an excellent discussion of the technic of the simpler hematologic examinations. The blood diseases are presented from the point of view of disturbances in the balance between blood formation, blood circulation and blood destruction, or localization in the tissues. Case reports are employed to illustrate the different categories in the classification employed. On the whole it is a brief stimulating presentation of an individual point of view on clinical hematology.

M. C. P.

## DR. ARTHUR LYNN ANDERSON

Dr. Arthur Lynn Anderson, Springfield, Missouri, died October 25, 1940, of cerebral hemorrhage. Dr. Anderson was born January 16, 1875, in Henry County, Kentucky. His academic college work was at William Jewell College, Liberty, Missouri. He received his medical degree from the University Medical College of Kansas City, Missouri, in 1900. After receiving his medical degree he practiced for seven years at Wilburton, Oklahoma, and from there he moved to Springfield, Missouri, where he practiced internal medicine for 33 years.

He was Consulting Internist at St. John's, Burge, and Springfield Baptist Hospitals and Missouri State Sanatorium. He was a member of the Greene County Medical Society, Missouri State Medical Association, Mississippi Valley Medical Society, Southern Medical Association, American Medical Association, and a Fellow of The American College of Physicians since 1924. During the first world war, Dr. Anderson volunteered and served in the Medical Corps at Camp Sevier, Greenville, S. C.

Dr. Anderson will be remembered by his colleagues as an expert diagnostician, honest with his patients and not believing in commercialism in the practice of medicine. He had a phenomenal memory for what he had read, and could recite his medical books almost page by page. He was good-natured, had a hearty infectious laugh and a kindly outlook on the world and was slow to criticize others. In the late years of his life his health was poor and his activities curtailed. He will be greatly missed by his fellows.

A. C. GRIFFITH, M.D., F.A.C.P.,  
Governor for Missouri

## DR. OLIVER THOMAS OSBORNE

Dr. Oliver Thomas Osborne, F.A.C.P., of New Haven, died on November 11, 1940. He was born in New Haven on November 14, 1862.

Dr. Osborne received his early education at New Haven High School, and at Yale University where he obtained his medical degree in 1884 and his M.A. in 1899. He did postgraduate work at the University of Leipzig in 1884-85 and began the practice of medicine in New Haven in 1886.

From 1891 to 1925 Dr. Osborne was a member of the faculty of Yale Medical School as instructor, assistant professor, and professor of materia medica. From 1925 until his death he was Professor Emeritus of Therapeutics.

Dr. Osborne's chief interest was in the treatment of tuberculosis. He was instrumental in the founding of the New Haven County Anti-Tuberculosis Association, now the Gaylord Farm Association of Wallingford, and was connected with that institution from the time of its founding in 1903, as director, chairman of the medical board and member of the executive board. He was one of the founders of the American Tuberculosis Association in 1904.

## COLLEGE NEWS NOTES

### NEW LIFE MEMBER

Dr. Arthur M. Master, F.A.C.P., New York, N. Y., became a Life Member of the American College of Physicians on November 7, 1940.

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### GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged:

#### *Books*

- Dr. Lewellys F. Barker, F.A.C.P., Baltimore, Md.—“Psychotherapy”;  
Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—12th, Second Series, Supplement to “Modern Drug Encyclopedia and Therapeutic Guide”;  
Dr. Elliott P. Joslin, F.A.C.P., Dr. Alexander Marble, F.A.C.P., Dr. Howard F. Root, F.A.C.P., and Dr. Priscilla White, F.A.C.P., all of Boston, Mass.—“Treatment of Diabetes Mellitus”;  
Dr. Peter J. Steincrohn (Associate), Hartford, Conn.—“More Years for the Asking”;  
Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa.—“Diagnosis and Treatment of Cardiovascular Disease,” Volumes I and II;  
Dr. Edward E. Cornwall, F.A.C.P. (deceased), Brooklyn, N. Y.—“A Clinical Treatise on Diseases of the Heart”—donated by Dr. William S. Hubbard, F.A.C.P., Philadelphia, Pa.

#### *Reprints*

- Dr. Benjamin R. Allison (Associate), Hewlett, L. I., N. Y.—2 reprints;  
Dr. Joseph George Bohorfoush (Associate), Madison, Wis.—1 reprint;  
Dr. George E. Farrar, Jr. (Associate), Philadelphia, Pa.—9 reprints;  
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;  
Dr. Irving Greenfield (Associate), Brooklyn, N. Y.—2 reprints;  
Dr. Morrill L. Ilsley, F.A.C.P., Claremont, Calif.—1 reprint;  
Dr. Thomas Arthur Johnson (Associate), Drexel Hill, Pa.—6 reprints;  
Dr. Vincent William Koch, F.A.C.P., Janesville, Wis.—1 reprint;  
Dr. James R. Lisa, F.A.C.P., New York, N. Y.—19 reprints;  
Dr. Louis Bonner Owens (Associate), Cincinnati, Ohio—1 reprint;  
Dr. Cecil O. Patterson (Associate), Dallas, Texas—5 reprints;  
Dr. Donald H. Root (Associate), Mendon, Ill.—1 reprint;  
Dr. Peter J. Steincrohn (Associate), Hartford, Conn.—4 reprints;  
Col. Edward B. Vedder, F.A.C.P., (MC), USA, Washington, D. C.—2 reprints;  
Dr. F. Eugene Zemp, F.A.C.P., Columbia, S. C.—1 reprint.

Among recent gifts to the College Library of publications by members is that of Volumes I and II, “Diagnosis and Treatment of Cardiovascular Disease,” published by the F. A. Davis Company, 1940, and edited by Dr. William D. Stroud, F.A.C.P., Philadelphia. Among the contributors appear the following members of the American College of Physicians:

Edgar V. Allen, F.A.C.P., Rochester, Minn.  
Joseph H. Barach, F.A.C.P., Pittsburgh, Pa.  
Nelson W. Barker, F.A.C.P., Rochester, Minn.



He also devoted himself to work in the field of stomatology and was at one time vice-president of the American Stomatological Association. In 1933 this Society awarded him the Chompret prize for his contributions to that science.

During his long and active career Dr. Osborne had been chief of the Medical Clinic of New Haven Dispensary, consultant to the New Haven Orphan Asylum, consulting physician to Griffin Hospital of Derby, President of the Yale Medical Alumni Association, Vice-President of the United States Pharmacopoeial Convention and member of the Revision Committee of the United States Pharmacopoeia, member of the Council on Pharmacy and Chemistry of the American Medical Association, Editor of the Therapeutic Section of the Journal of the American Medical Association, Chairman of the Section on Therapeutics of the American Medical Association.

He was a member of the New Haven County Medical Association, the New Haven Medical Association, Connecticut State Medical Society, Association of American Medical Editors, and the Association for the Study of Internal Secretions. Since 1923 he was a Fellow of the American College of Physicians and for several years was Governor of the College for Connecticut. Dr. Osborne took an active interest in the College and was directly responsible for its early growth in the State of Connecticut.

Dr. Osborne was well known for his numerous books and articles on medical subjects. Among his publications were "Handbook of Therapy," "Disturbances of the Heart," "Prevention and Treatment of Infections," "Disturbances of the Kidneys," "Principles of Therapeutics," "Introduction to Materia Medica and Prescription Writing," "Acromegaly: Buck's Reference Handbook of the Medical Sciences," Volume I, "Introduction to Materia Medica and Pharmacology," "Mouth Infection," "The Evaluation of Symptoms," "Gaylord Farm Sanatorium: Its Early History," and more than one hundred original articles on medical subjects published in various medical journals, the last appearing during the current year—1940.

He was a Mason and was also a member of the Graduates' Club, the Union League, Young Men's Republican Club, Quinnipiack Club, New Haven Chamber of Commerce, Connecticut Society for Mental Hygiene, Connecticut Academy of Arts and Sciences, and the New Haven Colony Historical Society.

Dr. Osborne is survived by his widow, Mrs. Mary Woodward Osborne, and one daughter, Miss Marguerite Nichols Osborne.

CHARLES H. TURKINGTON, M.D., F.A.C.P.,  
Governor for Connecticut

David P. Barr, F.A.C.P., St. Louis, Mo.  
Samuel Bellet (Associate), Philadelphia, Pa.  
Albert W. Bromer, F.A.C.P., New York, N. Y.  
Carl R. Comstock, F.A.C.P., Saratoga Springs, N. Y.  
Lewis A. Conner, F.A.C.P., New York, N. Y.  
Arthur C. De Graff, F.A.C.P., New York, N. Y.  
Thomas M. Durant, F.A.C.P., Philadelphia, Pa.  
Joseph M. Hayman, Jr., F.A.C.P., Cleveland, Ohio  
George Herrmann, F.A.C.P., Galveston, Tex.  
E. A. Hines, Jr., F.A.C.P., Rochester, Minn.  
W. R. Houston, F.A.C.P., Austin, Tex.  
William J. Kerr, F.A.C.P., San Francisco, Calif.  
John T. King, Jr., F.A.C.P., Baltimore, Md.  
Eugene M. Landis, F.A.C.P., Charlottesville, Va.  
Samuel A. Levine, F.A.C.P., Boston, Mass.  
Robert L. Levy, F.A.C.P., New York, N. Y.  
Alexander Margolies (Associate), Philadelphia, Pa.  
Currier McEwen, F.A.C.P., New York, N. Y.  
Thomas M. McMillan, F.A.C.P., Philadelphia, Pa.  
William R. Minnich, F.A.C.P., Atlanta, Ga.  
James E. Paullin, F.A.C.P., Atlanta, Ga.  
William B. Porter, F.A.C.P., Richmond, Va.  
Hugo Roesler, F.A.C.P., Philadelphia, Pa.  
Howard G. Schleiter, F.A.C.P., Pittsburgh, Pa.  
Fred M. Smith, F.A.C.P., Iowa City, Iowa  
Howard B. Sprague, F.A.C.P., Boston, Mass.  
Edward J. Stieglitz, F.A.C.P., Washington, D. C.  
William D. Stroud, F.A.C.P., Philadelphia, Pa.  
Henry M. Thomas, Jr., F.A.C.P., Baltimore, Md.  
Joseph B. Vander Veer (Associate), Philadelphia, Pa.  
Soma Weiss, F.A.C.P., Boston, Mass.  
Paul D. White, F.A.C.P., Boston, Mass.  
Frank N. Wilson, F.A.C.P., Ann Arbor, Mich.  
Charles C. Wolferth, F.A.C.P., Philadelphia, Pa.  
Irving S. Wright, F.A.C.P., New York, N. Y.

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#### WEST VIRGINIA MEETING OF MEMBERS

During July of the current year members of the College in Virginia and members of the College in West Virginia held a joint luncheon and a joint session at White Sulphur Springs, W. Va., presided over by Dr. Albert H. Hoge, College Governor for West Virginia, and Dr. Walter B. Martin, College Governor for Virginia. There were some guests and the meeting was well attended by the members.

On October 29, in connection with a meeting of the West Virginia Heart Association at Charleston, members of the College of the State held a get-together luncheon at the Daniel Boone Hotel, where there was a good attendance and general discussion of College matters. A committee was appointed to study the matter of a formal state meeting of members, with a scientific program as well as the social aspects. The College members in West Virginia are naturally relatively small in number and widely scattered, and heretofore no formal meetings with scientific programs have been held in this State, as is the custom in some of the larger and more highly populated centers.

# POSTGRADUATE FACILITIES IN INTERNAL MEDICINE AND ALLIED SUBJECTS

In accordance with directions of the Board of Regents of the American College of Physicians, there will be published in the ANNALS OF INTERNAL MEDICINE from time to time listings of available educational opportunities in Internal Medicine and the allied specialties, particularly from the standpoint of Postgraduate Courses. The first listing appeared in the September, 1940, issue, and the following listing eliminates those courses that have already been given during the past three months. However, there are added additional courses and other announcements that have been collected during the interim.

For greater details concerning courses or postgraduate meetings, consult the institutions.

## Part I—Graduate Institutions

Columbia University  
New York Post-Graduate Medical School and Hospital  
Irving S. Wright, M.D., Executive Officer  
301 E. 20th Street  
New York, N. Y.

### *Part-time Courses:*

A number of courses in the field of medicine are offered three times during the year, beginning with the week of January 2, 1941 and April 1, 1941. Courses consist of lectures and clinical demonstrations, stressing the diagnosis and treatment of the various disease conditions.

#### 301—*Arthritis and Rheumatic Diseases*

Two months; 9:00 a.m. to 12:00 m., Tuesdays; Fee, \$35.00.

#### 303—*Cardiology*

Two months; 2:00 to 5:00 p.m., Mondays; Fee, \$35.00.

#### 304—*Clinical Interpretations of Laboratory Data*

Two months; 9:00 to 11:00 a.m., Wednesdays; Fee, \$25.00.

#### 307—*Diagnosis*

Two months; 9:00 a.m. to 12:00 m., Mondays; Fee, \$35.00.

#### 308—*Diseases of the Chest*

Two months; 9:00 a.m. to 12:00 m., Thursdays; Fee, \$35.00.

#### 309—*Diseases of the Thyroid and Other Endocrine Glands, and Obesity*

Two months; 9:00 a.m. to 12:00 m., Fridays; Fee, \$35.00.

#### 310—*Diseases of the Liver and Biliary Tract*

Two months; 11:00 a.m. to 1:00 p.m., Wednesdays; Fee, \$25.00.

#### 311—*Gastro-enterology*

Two months; 2:00 to 5:00 p.m., Wednesdays; Fee, \$35.00.

#### 312—*Clinical Hematology*

Two months; 3:00 to 4:00 p.m., Fridays; Fee, \$15.00.

## FALL MEETING OF MARYLAND MEMBERS OF THE COLLEGE

Fellows and Associates of the College residing in Maryland customarily hold two regional meetings each year. The 1940 fall meeting was held Tuesday, December 3, at the Belvedere Hotel in Baltimore under the Chairmanship of Dr. Wetherbee Fort and the Secretaryship of Dr. R. Carmichael Tilghman. Dr. Louis Krause, of Baltimore, is the College Governor for Maryland. The Maryland group, or "chapter," elects annually a President and Secretary, and Drs. Fort and Tilghman, respectively, hold those offices during the current year.

The Committee on Arrangements include, in addition to Drs. Fort and Tilghman, Dr. George M. Settle, Dr. Moses Paulson, Dr. Walter L. Winkenwerder, Dr. T. Nelson Carey. The meeting was initiated by a social hour and dinner, with Dr. Fort acting as Toastmaster. Dr. Richard A. Kern, F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine and Graduate School of Medicine, Chief of Allergy Section, Chief of Outpatient Department and Visiting Ward Physician to the Hospital of the University of Pennsylvania, Philadelphia, presented an address on "Clinical Allergy." Dr. Edward L. Bortz, F.A.C.P., Chairman of the Advisory Committee on Postgraduate Courses and Governor for Eastern Pennsylvania, A. C. P., Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine, Chief of Medical Service B, Lankenau Hospital and President of the Philadelphia County Medical Society, spoke on "Graduate Study and the American College of Physicians."

The attendance was the largest of any of the regional meetings previously held in Maryland and the program was enthusiastically received.

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Dr. Sidney A. Slater, F.A.C.P., Worthington, Minn., Superintendent of the Southwestern Minnesota Sanatorium, was reelected president of the Minnesota Public Health Association at the annual meeting held in St. Paul, Minn., in conjunction with the 27th annual meeting of the Mississippi Valley Conference on Tuberculosis.

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Dr. Henry R. Carstens, F.A.C.P., Detroit, Mich., was elected president-elect of the Michigan State Medical Society at their 75th annual session in Detroit, September 24-27, 1940. Dr. Theodore I. Bauer, F.A.C.P., Lansing, Mich., was elected chairman and Dr. Gordon B. Myers, F.A.C.P., Detroit, Mich., secretary, of the Medical Section of this Society.

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Dr. Albert S. Hyman, F.A.C.P., New York, N. Y., was recently elected President of the U. S. Naval Reserve Medical Officers Association. This Association comprises all of the Medical and Dental Reserve Officers in the Third Naval District. Dr. Hyman is a Lieutenant Commander in the Reserve Medical Corps and Consultant Cardiologist to the Third Naval District.

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Dr. Frederick L. Brown, F.A.C.P., and Dr. Karl Rothschild, F.A.C.P., both of New Brunswick, N. J., have been appointed members of the Medical Advisory Committee to the Selective Service Boards of New Jersey by Governor A. Harry Moore. Dr. Brown will serve as Internist and Dr. Rothschild as Neuropsychiatrist for the Counties of Middlesex and Monmouth.

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Dr. George Herrmann, F.A.C.P., Galveston, Texas, Professor of Medicine at the University of Texas Medical School, presented a paper on "The Modern Treatment of Congestive Heart Failure" at the recent meeting of the Inter-State Post-Graduate Assembly of North America in Cleveland, Ohio.

313—*Diabetes Mellitus and Nephritis*

Two months; 2:00 to 5:00 p.m., Thursdays; Fee, \$35.00.

315—*Psychological Aspects of Internal Medicine*

Two months; 4:00 to 5:00 p.m., Fridays; Fee, \$15.00.

318—*Pulmonary Tuberculosis*

Two months; 9:00 a.m. to 12:00 m., Saturdays; Fee, \$35.00.

319—*Peripheral Vascular Diseases*

Two months; 2:00 to 4:00 p.m., Tuesdays; Fee, \$25.00.

335—*Electrocardiography*

Two two-hour sessions weekly for four weeks; 9:00 to 11:00 a.m., Tuesdays and Thursdays; April 1-24, 1941; Fee, \$75.00.

344—*Advanced Electrocardiography*

Two two-hour sessions weekly for four weeks; 9:00 to 11:00 a.m., Tuesdays and Thursdays; April 29-May 22, 1941; Fee, \$100.00.

*Full-time Courses*300—*Seminar in Internal Medicine*

Two months; Fee, \$125.00 for one month; \$200.00 for two months.

330—*Arthritis and Rheumatic Diseases*

Five days; April 14-18, 1941; Fee, \$35.00.

331—*Allergy*

Three weeks; April 14-May 2, 1941; Fee, \$150.00.

332—*Cardiovascular Diseases*

Four weeks; March 3-29, 1941; Fee, \$125.00.

334—*Endocrinology*

Ten days; March 3-14, 1941; Fee, \$50.00.

336—*Gastro-enterology*

Three weeks; March 3-22, 1941; Fee, \$75.00.

337—*Diabetes Mellitus, Nephritis and Hypertension*

Five days; April 21-25, 1941; Fee, \$35.00.

341—*Symposium in Medicine*

Ten days; June 9-20, 1941; Fee, \$30.00 for five days; \$50.00 for ten days.

342—*Physical Diagnosis*

Ten days; January 13-24, 1941; Fee, \$50.00.

347—*Clinical Interpretations of Laboratory Data*

Five days; June 2-6, 1941; Fee, \$35.00.

348—*Tropical Medicine*

Five days; May 19-23, 1941; Fee, \$50.00.

350—*Pulmonary Tuberculosis*

Four weeks; May 1-29, 1941; Fee, \$100.00.

351—*Symposium on the Clinical Applications of Chemotherapy and Vitamins*

Five days; February 24-28, 1941; Fee, \$35.00.

20. SEVIER, CHARLES E.: Treatment of chronic arthritis from the orthopedic standpoint, *Colorado Med.*, 1936, xxxii, 101.
21. OBER, FRANK R., and GREEN, WM. T.: The care of joints in chronic proliferative arthritis of children, *Jr. Am. Med. Assoc.*, 1934, ciii, 1732.
22. TIMBRELL FISHER, A. G.: The principles of orthopedic and surgical treatment in the rheumatoid type of arthritis, *Jr. Bone and Joint Surg.*, 1937, xix, 657.
23. ANOPOL, GEO.: Functional position from the orthopedic standpoint, *Am. Jr. Surg.*, 1932, xv, 63.
24. JONES, SIR ROBERT, and LOVETT, ROBERT W.: *Orthopedic surgery*, 2nd Edition, 1933, William Wood and Co., Baltimore, p. 722.
25. STUMP, JOHN P.: What the orthopedist can do for the arthritic, *New York State Jr. Med.*, 1933, xxxiii, 998-999.
26. LLOYD-WILLIAMS, I. H.: Arthritis deformans and its treatment by manipulation, *Am. Jr. Phys. Therap.*, 1931, i, 497.
27. IRISH, WM. H., and STUMP, JOHN P.: Villous synovitis of the knees due to improper distribution of weight, *Arch. Phys. Therap.*, 1939, xx, 391-396, 405.
28. COTTON, FRED. J.: Knee lesions and operations based on 100 personal cases, *Surg. Clin. North Am.*, 1922, ii, 1021.
29. DAVIDSON, L. S. P.: Chronic infective arthritis. Reports on chronic rheumatic diseases, No. 2, 1936, The Macmillan Co., New York, p. 22.
30. ANOPOL, GEO.: Mechanics in weak and flat feet, *Am. Jr. Surg.*, 1929, viii, 256.
31. THORNDIKE, A., JR., and GARREY, W. E.: A useful type of light, waterproof cast, *New England Jr. Med.*, 1938, ccxviii, 205.
32. EWERHARDT, F. H.: Physical means in the treatment of arthritis, *Jr. Missouri Med. Assoc.*, 1929, xxvi, 7.
33. SWAIM, LORING T.: The orthopedic and physical therapeutic treatment of chronic arthritis, *Jr. Am. Med. Assoc.*, 1934, ciii, 1589.
34. YATER, WALLACE M.: The general practitioner's concept of the treatment of arthritis, *Med. Ann. District of Columbia*, 1935, iv, 4.
35. SWAIM, L. T., and KUHNS, J. G.: The prevention of deformities in chronic arthritis. I. The upper extremity, *Jr. Am. Med. Assoc.*, 1929, xciii, 1853. II. The spine and the head, *Jr. Am. Med. Assoc.*, 1930, xciv, 1123. III. The lower extremity, *Jr. Am. Med. Assoc.*, 1930, xciv, 1743.
36. MINOT, GEO. R.: General aspects of the treatment of chronic arthritis, *New England Jr. Med.*, 1933, ccviii, 1285.
37. FAHLSTROM, STANLEY: Treatment of arthritis, *Arch. Phys. Therap.*, 1931, xii, 96.
38. COULTER, JOHN S.: Physical therapy in chronic rheumatic diseases, *New Orleans Med. and Surg. Jr.*, 1936, lxxxix, 195.
39. KOVACS, RICHARD, and KOVACS, JOSEPH: Chronic arthritis: recent problems of its structural changes with special reference to physical therapy, *Arch. Phys. Therap.*, 1934, xv, 227.
40. CURRENCE, JOHN D.: Hydrotherapy in arthritic and rheumatic affections, *Arch. Phys. Therap.*, 1933, xiv, 197.
41. SMITH, EUCLID M.: Underwater therapy in chronic arthritis, *Arch. Phys. Therap.*, 1935, xvi, 534.

# CARDIAC ANEURYSM

## A Report of Ten Cases \*

By WILHELM DRESSLER, M.D., *New York City*, and ROBERT PFEIFFER, M.D., *Vienna*

### INTRODUCTION

CARDIAC aneurysm is not a rare finding on postmortem examination. Clinicians of the older generations were well aware of this and, in view of the seriousness of the condition, their eager search for clinical signs and symptoms by which it might be recognized during life was easily understandable.

Beginning with the middle of the last century, numerous medical reports are available, referring particularly to the findings by physical examination. Huchard<sup>1</sup> suggested that a very large area of cardiac dullness in subjects affected by arteriosclerosis might point towards the existence of a cardiac aneurysm. Abnormal sounds and musical murmurs, humming, blowing or whistling, either systolic or diastolic, were repeatedly mentioned as valuable aids to diagnosis. Their presence was attributed to the flow of blood through a narrowed opening leading into the aneurysmal sac. Huchard thought that a post-systolic murmur audible only over the apical region, in association with certain other physical signs, was a useful sign in the diagnosis of cardiac aneurysm. Also a gallop rhythm was often mentioned as indicative of this condition. Lutembacher<sup>2</sup> stressed the significance of a continuous, rather severe pain limited to a well defined area in the apical region. Pulsatory phenomena, as obtained by palpation, have played a considerable part in all diagnostic inquiries. Kasem-Beck<sup>3</sup> stated that a heavy cardiac thrust, associated with a feeble pulse, was a reliable sign in diagnosis. Huchard<sup>1</sup> described, as a characteristic finding, an intensified cardiac thrust particularly marked over the precordium but absent in the apical region.

In spite of all these observations some of the eminent clinicians have repeatedly expressed very skeptical opinions as to the diagnostic value of the signs reported. Hall<sup>4</sup> wrote in 1903: "Aneurysm of the heart must necessarily be of interest rather to the pathologist than to the clinician, for they are outside of the pale of practical diagnosis." Sternberg<sup>5</sup> stated in 1914 that out of 300 cases published up to the time at which he was writing, only two had been diagnosed during life. Hence he concluded that physical signs were worthless in diagnosis of cardiac aneurysm. Lutembacher<sup>2</sup> held the same view, and Christian and Frick<sup>6</sup> wrote in 1922: "The diagnosis of

\* Received for publication May 17, 1939.

Presented in part at the Society for Internal Medicine in Vienna (Mitt. d. Gesellsch. f. inn. Med. u. Kinderh., 1935, xxxiv, 171).

In addition to these part-time and full-time courses, the New York Post-Graduate Medical School has scheduled similar courses in neurology and psychiatry, pathology, pediatrics, bacteriology, dermatology and syphilology.

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Cook County Graduate School of Medicine  
James F. Askin, Registrar  
427 S. Honore St.  
Chicago, Ill.

*Allergy*—Monthly Course, starting first day of each month. Personal course. Fee, \$200.00.

*Electrocardiography and Heart Disease*—Monthly Course, starting first day of each month, except August and December. Fee, \$175.00.

*Electrocardiography and Heart Disease*—First Monday in August, 1941. Two-weeks intensive personal course. Fee, \$150.00.

*Gastro-enterology*—April (2 weeks), 1941. Two-weeks intensive course, offered each April and October. Fee, \$125.00.

*Internal Medicine*—April 7-19, 1941. A general course presented by members of the medical faculty; includes lectures, demonstrations and conferences. This course is offered for periods of two weeks starting with the first Monday in October and April. Fee, \$75.00.

*Internal Medicine*—By appointment. Intensive personal course of ten or twenty hours on selected subjects. Fee, according to hours.

*Modern Treatment of Pneumonia*—By appointment, three or four times yearly. One-week intensive personal course given by Dr. Italo F. Volini, F.A.C.P. Fee, by arrangement.

*Roentgenology*—Starts every Monday.

Courses in roentgen-ray diagnosis, fluoroscopy and therapy. Fee, by arrangement.

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New York Polyclinic Medical School and Hospital  
F. H. Dillingham, M.D., Medical Executive Officer  
341-53 W. Fiftieth Street  
New York, N. Y.

#### 110—*Medicine*

Full-time Course; six weeks; integrated clinical and didactic study; fundamental theories applied in clinic; practical problems in diagnosis and treatment; demonstrations in medical specialties, including cardiology, allergy, arthritis, tuberculosis, diabetes and metabolism, gastro-enterology, pediatrics, neuropsychiatry and dermatology and syphilology.

The matriculant may supplement the course by an additional six weeks of actual work in the wards and outpatient department of the hospital. Dates and fees not announced.

#### *Pediatrics*

This institution is prepared to offer two courses in this field, one in general pediatrics and one in endocrine diseases and disorders of infants, children and adolescents.

Dates of the courses and fees were not announced.



Observation courses have been organized by the Medical Faculty and Staff of the State of Wisconsin General Hospital upon the approval of the Regents of the University of Wisconsin. No stereotyped courses or lectures are afforded, but attendance upon lectures, clinical services and staff meetings of the Hospital is arranged. A stated fee is charged all physicians in attendance upon the clinical services for periods exceeding one (1) month. This fee shall be \$100.00 per month or \$400.00 per semester and shall be credited to the department to which the physician is assigned. A certificate of attendance shall be granted upon the completion of the course and shall be signed by the President, Dean of the Medical School and chief of the responsible department. No credit toward an advanced degree may be earned by such attendance, nor is it purposed to include the existing residencies in the scope of this recommendation.

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Vanderbilt University School of Medicine  
John B. Youmans, M.D., Department of Medicine  
Nashville, Tenn.

### 1. Medicine

These courses, which are designed primarily for the holders of Commonwealth Fund fellowships, are given during the summer from approximately mid-June to mid-July. The course is of one month's duration and consists of seminars, conferences and practice work in the wards and the outpatient department in Internal Medicine and allied specialties of dermatology, neurology, psychiatry, metabolic diseases, allergy, diseases of the chest and syphilis.

It is designed to review this field for the general practitioner and acquaint him with the advances in diagnosis and treatment. A limited number of physicians in addition to the holders of Commonwealth Fund fellowships will be accepted under certain conditions. Tuition, \$50.00.

### 2. Syphilis—Medicine 12. *For County Health Officers and Physicians with Appointment in Public Health Units*

This course is open to county health officers and physicians with appointments in public health units. It is designed to familiarize the health officer with all aspects of the syphilis problem. It offers him the opportunity of studying the individual patient, history taking, physical examination, darkfield and lumbar puncture procedures and treatment.

The student attends each clinic session for a period of four weeks and assists in the conduct of the clinic. A series of lectures early in the course is given to review the clinical and epidemiological aspects of syphilis. The remainder of the time is devoted to field work, under the direction of the epidemiologist. Several such courses are given from September to April inclusive. Each course is limited to six physicians. No tuition fee.

### 3. Syphilis—Medicine 13. *Postgraduate Course in Syphilis*

This course is open to properly qualified physicians wishing to secure special training in syphilis. It is designed to offer training fitting the student for positions of responsibility in syphilis control work.

The physician is expected to take his place as one of the staff of the clinic, to examine and treat his patients, assuming responsibility for them. Opportunity for thorough training is offered in the conduct of a syphilis clinic, the diagnosis of the disease, including darkfield and lumbar puncture

*Dermatology and Syphilology*

140—*Practical Instruction in Dermatology and Syphilology*  
Six weeks; dates and fees not announced.

141—*Advanced Course in Dermatology and Syphilology*  
Three months; dates and fees not announced.

142—*Syphilology*  
Six weeks; dates and fees not announced.

*Gastro-enterology*

170—*Combined Course in Proctology, Gastro-enterology and Allied Subjects*  
Six weeks; dates and fees not announced.

173—*Clinical Gastro-enterology, for the General Practitioner*  
Six weeks; dates and fees not announced.

*Neuropsychiatry*

A general course is announced, though dates and fees are not given.

*Pathology and Bacteriology*

182—*Blood Transfusions*  
A short course; dates and fees not announced.

*Roentgenology*

190—*Practical Roentgenological Interpretation and Technic*  
Three months, or shorter courses by special arrangement; dates and fees not announced.

## University of Pennsylvania Graduate School of Medicine

George H. Meeker, Ph.D., Dean

36th & Pine Streets

Philadelphia, Pa.

This institution does not schedule short intensive courses, but offers basic study courses in the major clinical departments. A fee of \$800.00 is required for the basic studies in any one of the major clinical departments. There are no fees for continuation studies leading to the Master's and Doctor's degrees for candidates who have previously paid fees for underlying basic clinical studies. When the Master's degree is conferred, for continuation clinical and thesis studies, there is a graduation fee of \$100.00. All the following basic study courses require eight months and are given from October to June annually: internal medicine, pediatrics, neurology-psychiatry, dermatology-syphilology, radiology.

The Graduate School of the University of Pennsylvania also sponsors "personal courses," designed to furnish to physicians relatively brief opportunities for miscellaneous studies in subdepartmental subjects. Academic credits are not involved. Fees for personal courses are arbitrary, and are not affected by the total hours, or time periods, involved in actual work.

## TABULATION OF PERSONAL COURSES

*Cardiology*—William D. Stroud, M.D., Professor of Cardiology.

8 Thursdays, 52 hours, courses beginning the first Thursday of October, January and April; Fee, \$80.00.

procedures and in treatment. Epidemiological field work is to be done under the direction of the epidemiologist of the syphilis clinic.

Physicians will be accepted for such work for a period of six to twelve months, dependent upon the needs of the individual physician. No tuition fee.

4. *Syphilis B. Demonstration in Syphilis Clinic Management for Physicians and Nurses*

This course is open to physicians and registered nurses. It is designed to give an opportunity to physicians and nurses to observe the management of patients and clinic procedures for a period of two weeks at intervals during the year. Several such courses are given from September to April inclusive. No more than three physicians and two nurses will be accepted during each period. No tuition fee.

5. *Graduate Course in Internal Medicine*

This course consists of supervised work with patients in the medical outpatient service, including the related specialties; experience in the diagnostic laboratories; assigned reading, seminars and conferences, including pathological and radiological conferences and autopsy study; directed study and seminars in the pre-clinical sciences, particularly physiology and biochemistry. Special investigation of a particular problem in one of the divisions of internal medicine as the basis of a thesis is required. The course extends over a period of one year and is open to physicians who have completed an internship, have had an additional year's experience as assistant resident in medicine or its equivalent and are acceptable to the school. Courses begin July 1 and are limited to six students. Tuition fee, \$300.00.

*Fellowships*

Three fellowships are available for this course described above. These fellowships, which provide tuition, board and lodging, are open to those who meet the requirements mentioned above and will be awarded on the basis of the individual's training and recommendations.

6. *Special work in the Department of Medicine may be made available by special arrangement.*

Tuition and fees according to arrangement.

Further information regarding these courses should be addressed to the Registrar of the School of Medicine, Vanderbilt University, Nashville, Tenn.

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Woman's Medical College of Pennsylvania

Dr. Margaret D. Craighill, Acting Dean

Henry Ave. & Abbottsford Rd.

East Falls, Philadelphia, Pa.

This institution offers but one postgraduate course. This is an intensive course of two weeks' duration in electrocardiographic technic given during the summer months, if five registrants are obtained. Fee, \$100.00.

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Yale University School of Medicine

333 Cedar St.

New Haven, Conn.

Any physician of good standing in the community may on application to the head of a department in the Yale University School of Medicine obtain permission to attend clinics, lectures, conferences or ward rounds; or to do special work in association

*Parasitology and Tropical Medicine*—Damaso deRivas, M.D., Professor of Parasitology.

6 weeks, 150 hours; Fee, \$125.00.

*Clinical Gastro-enterology*—H. L. Bockus, M.D., Professor of Gastro-enterology.

16 weeks, 500 hours; Fee, \$400.00.

*Allergy*—H. B. Wilmer, M.D., Associate Professor of Allergy.

4 weeks, 40 hours; Fee, \$150.00.

*Diabetes Mellitus*—Edward S. Dillon, M.D., Assistant Professor of Diseases of Metabolism.

2 to 4 weeks, 75 hours; Fee, \$150.00.

*Clinical Psychiatry*—S. DeW. Ludlum, M.D., Professor of Psychiatry.

8 weeks, 240 hours; Fee, \$160.00.

*Clinico-biologic Neurology and Psychiatry*—D. W. Bronk, Ph.D., Professor of Neurology; Earl D. Bond, M.D., Professor of Psychiatry; and Associates.

10 weeks, 250 hours; Fee, \$100.00.

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## Part II—Other Medical Colleges

Indiana University Medical Center

C. J. Clark, M.D., Chairman

Dept. of Medical Economics and Postgraduate Instruction

1040-1232 W. Michigan St.

Indianapolis, Indiana

*Newer Methods of Diagnosis and Treatment*—April 28 to May 2, 1941.

Comprehensive consideration of diagnosis and treatment with particular reference to newer methods; mornings devoted to clinics, afternoons to didactic suggestions; nationally prominent speaker will conduct a clinic or round-table each afternoon, and give an address in the evening. Fee, none.

*Pediatrics*—Each Wednesday, March, 1941.

Meetings will begin at 1:00 p.m. each Wednesday; a round-table dinner meeting each evening. Fee, none.

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Johns Hopkins University School of Medicine

Alan M. Chesney, M.D., Dean

710 N. Washington St.

Baltimore, Md.

No specific schedule of formal graduate courses is offered. However, the School of Medicine offers to a limited number of graduates in medicine opportunities for study in the various departments. Candidates desiring to avail themselves of these opportunities must be acceptable to the heads of the departments in which they wish to work; qualified candidates must enroll for periods of three academic quarters of two months each as a minimum, and preferably for a complete academic year; these opportunities for study are chiefly in the clinical departments, where the graduates will assist in the care of outpatients, doing a certain amount of laboratory study and occasionally undertaking an investigation in the history rooms or in the clinics

with the laboratories connected with the various departments. The institution lists opportunities for observation in medicine, pediatrics, psychiatry, pathology, public health, child development and the surgical specialties, giving hours of ward rounds, staff conferences, seminars, demonstrations, etc. There are no formally organized postgraduate courses announced.

### Part III—Postgraduate and Clinical Meetings

The American College of Physicians  
4200 Pine Street  
Philadelphia, Pa.

For Postgraduate Courses offered under the auspices of the American College of Physicians consult formal announcement appearing at the end of this section concerning the bulletin of Postgraduate Courses for the winter and spring of 1941.

The Twenty-Fifth Annual Session of the College, covering internal medicine and its allied specialties and consisting of General Sessions, Special Lectures, Panel Discussions, Clinics and Demonstrations, will be held in Boston, April 21–25, 1941, with headquarters at the Statler Hotel.

The Annual Sessions of the College are considered the most important conferences on Internal Medicine held in North America each year. These annual meetings constitute one of the most important activities of the College and afford members an opportunity of keeping informed of the most important and most recent developments in Internal Medicine and its allied specialties, such as Pediatrics, Neurology, Psychiatry, Pathology, Radiology, etc. This is the first time the College has held its annual meeting in Boston since 1929. During the interim, Boston has expanded its medical facilities and extended its medical personnel. Associates of the College are expected to attend at least one Annual Session as an evidence of their interest in the College and in Internal Medicine before coming up for advancement to Fellowship. Non-members of the College may also attend the meeting on the payment of a nominal registration fee. National medical meetings, especially of the character of those arranged by the College, constitute one of the most important armamentaria for medical progress. Contact with colleagues eager to learn, listening to discussions by those capable of teaching, witnessing demonstrations and clinics, viewing exhibits lead to more reading and better observation of patients. Herein lies medical progress. The meeting of the American College of Physicians provides just these opportunities. Attendance at this meeting is a potent way for a physician to get himself out of the group of those who each year know less. The stimulus received from attendance at a medical meeting where men eminent in the profession speak lasts long after the meeting is over.

Dallas Southern Clinical Society  
1133 Medical Arts Bldg.  
Dallas, Texas

The Dallas Southern Clinical Society will hold its 13th Annual Spring Clinical Conference in Dallas at the Hotel Adolphus, March 17–20, 1941. The meeting will consist of general assemblies, postgraduate teaching, clinics, round tables, clinical-pathological conferences, and scientific and technical exhibits. Among the guest speakers in the specialties indicated will be the following:

Dr. C. J. Barborka, Chicago .....Medicine  
Dr. W. Edw. Chamberlain, Philadelphia .....Radiology  
Dr. Harry Goldblatt, Cleveland .....Pathology

and laboratories; courses of study are largely individualized, according to needs of candidate; fee, \$50.00 each academic quarter.

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New York Medical College  
Claude A. Burrett, M.D., Dean  
5th Ave. at 105th St.  
New York, N. Y.

*Plan A:*

Opportunities for systematic training, leading to a graduate degree and extending over a period of three years, are offered to approved physicians who wish to qualify for practice in such clinical specialties as medicine, pediatrics, radiology and other branches; in order to qualify for a graduate degree candidates must satisfactorily complete three sessions or periods of study, each of approximately a year's duration—one year as a non-resident fellow devoted to theory and fundamentals, and two years in clinical practice and research as a hospital resident; candidates must pass oral and written examinations and satisfy all other requirements, including the completion of a research problem.

The bulletin outlines specific courses leading to the degree of Master of Science in Medicine in *Internal Medicine*, *Pediatrics* and *Radiology*, as well as some of the surgical specialties. The education committee is convinced that those who successfully complete these courses will be prepared for examination by the various American Specialty Boards.

Matriculation fee, \$10.00; tuition fee, first session, \$400.00; no fee when in residency; graduation fee, \$35.00.

*Plan B:*

Short courses by various College and Hospital departments to provide opportunities for practicing physicians to become familiar with new methods and technics; not credited toward a degree.

*Electrocardiography*—David Scherf, M.D., in charge.

Twenty conferences; June 16 to 30, 1941; fee, \$100.00.

*Clinical Cardiology*—David Scherf, M.D., in charge.

Twenty conferences; June 16 to 30, 1941; fee, \$100.00.

*Tuberculosis*—George Ornstein, M.D., and Staff.

May 1–31, 1941; fee, \$100.00.

*Physical Diagnosis*—Herbert Elias, M.D., in charge.

Twenty conferences; June 16 to 30, 1941; fee, \$100.00.

*Clinical Hematology*—Louis Greenwald, M.D., in charge.

Twenty conferences; June 16 to 30, 1941; fee, \$100.00.

*Management of the Diabetic*—Thomas H. McGavack, M.D., in charge.

Twenty conferences; June 16 to 30, 1941; fee, \$100.00.

*Endocrinology*—Thomas H. McGavack, M.D., in charge.

Twenty conferences; June 16 to 30, 1941; fee, \$100.00.

All courses given at New York Medical College and Metropolitan Hospital, except Tuberculosis, which will be given at Metropolitan and Sea View Hospitals.

Dr. Henry G. Poncher, Chicago .....Pediatrics  
 Dr. Marion B. Sulzberger, New York .....Dermatology  
 Dr. Soma Weiss, Boston .....Medicine

These speakers will appear daily in general assemblies, clinics, and symposia. In addition, local members of the profession will present a series of postgraduate lectures and one afternoon of clinics and symposia.

Any physician who is a member of his county medical society may register. Registration fee, \$10.00.

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Philadelphia County Medical Society  
 21st & Spruce Sts.  
 Philadelphia, Pa.

The 6th Annual Postgraduate Institute of the Philadelphia County Medical Society, under the direction of Rufus S. Reeves, M.D., will be held in Philadelphia at the Bellevue-Stratford Hotel, March 31 to April 4, 1941. The subject of this Postgraduate Institute will be "Symposia on Modern Therapy," and will cover immunology, pediatrics, dermatology, gastro-enterology, physiotherapy, allergy, chemotherapy, the avitaminoses, roentgen-ray therapy, pneumonia and upper respiratory infections, the acute infections, and gynecology. The program will be made up of speakers whose work is authoritative, who are members of the various medical schools, and who are members of the Philadelphia County Medical Society.

All members of a county medical society in good standing are eligible for registration. Fee, \$5.00.

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## POSTGRADUATE COURSES ARRANGED BY THE AMERICAN COLLEGE OF PHYSICIANS

### Winter and Spring of 1941

The Advisory Committee on Postgraduate Courses and the Committee on Educational Policy of the American College of Physicians announce the following courses, arranged through the generous coöperation of the directors and the institutions at which the courses will be given.

This is the fourth year of this activity by the College. The courses are offered especially for Fellows and Associates of the College, but where facilities are available, they are open to those preparing either to meet the requirements for membership in the College or certification by the American Board of Internal Medicine.

The courses are made available by the College to its members at minimum cost, because the College itself has assumed full responsibility for promotion, advertising, printing and registration as its contribution. This schedule of courses is announced after a complete survey of the needs and wishes of the College members. Due to a growing demand for courses at other periods of the year than just preceding the Annual Session, the College has initiated this year two courses in February and plans to extend the schedule to other seasons of the year in succeeding years, if the demand for such courses justifies this extension. The number of courses to be given as pre-meeting courses, just preceding the Twenty-fifth Annual Session at Boston, April 21-25, has been extended and the type of courses has been selected according to the recommendations of the membership.

*Fees*—The registration fee, regardless of the institution or course selected, is based on \$20.00 for each week. One-half of the registration fee is payable at time

New York University College of Medicine  
Currier McEwen, M.D., Dean  
477 1st Ave.  
New York, N. Y.

*Graduate Study of Medicine—three-year full-time course.*

A limited number of recent graduates in medicine who have had at least two years' internship or its equivalent will be admitted to this course in internal medicine; problems pertaining to the basic medical sciences as applied to clinical medicine are developed by the students under the guidance of a member of the faculty and in conjunction with other departments, according to the nature of the study; fee, \$12.00 for each year of work.

*Short Courses*

*Internal Medicine*

Five mornings per week for a period of one month; each month constitutes a complete session; eight sessions during the year, from October through May; fee, per session, \$50.00.

Course designed for physicians in general practice desiring a practical review of recent advances in diagnosis and treatment; instruction will be given to small groups.

*Clinical Electrocardiography*

Fifteen weeks, 2:30 to 4:30 p.m., Mondays; February 3–May 12, 1941; fee, \$50.00.

Interpretation of the electrocardiogram and its practical application; measurement and analysis of a large number of curves; operation of standard instruments; normal and abnormal electrocardiograms; Louis F. Bishop, Jr., M.D., Director; courses given by the Fourth Medical Division of Bellevue Hospital.

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Northwestern University  
J. Roscoe Miller, M.D., Director of Courses  
303 E. Chicago Ave.  
Chicago, Ill.

This institution conducts postgraduate courses in gastro-enterology, cardio-renal-vascular medicine, endocrinology and hematology by short intensive courses of from six to twelve days, with fee of \$25.00 for one-week courses and fee of \$50.00 for two-week courses; late August and early September schedule already completed; no announcement at hand for repetition of these courses later in year.

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Stanford University School of Medicine  
L. R. Chandler, M.D., Dean  
2398 Sacramento St.  
San Francisco, Calif.

This institution conducts postgraduate medical courses for practicing physicians in coöperation with the San Francisco Department of Public Health and the San Francisco Hospital; courses of one-week duration are given each year and those for 1940 have already been completed; bulletin listed pediatrics, gastro-enterology, management of hypertension and nephritis, roentgen-ray diagnosis and therapy.



of registration and the balance shall be paid not later than one week in advance of the opening of any course.

The College will record all registrations with the respective institutions offering courses and will directly reimburse those institutions for each student-physician at the specified fee. A matriculation card will be sent each registrant when his fee has been paid in full.

## REVISED SCHEDULE

### February Courses

#### *St. Louis, Mo.*

Dr. Harry L. Alexander, Director

- Course No. 1. Allergy—Washington University School of Medicine  
(2 weeks—February 10 to 21, 1941)

#### *New York, N. Y.*

Dr. Robert A. Cooke, Director

- Course No. 2. Allergy—The Roosevelt Hospital, Department of Allergy  
(2 weeks—February 10-21, 1941)

#### *Rochester, Minn.*

Dr. Edgar V. Allen, Director

- Course No. 3. Gastro-enterology—Mayo Foundation of the University of Minnesota  
(2 weeks—February 10 to 22, 1941)

### Pre-Meeting Courses

#### *Boston, Mass.*

Drs. Means, Minot, Weiss and Monroe, Directors

- Course No. 4. Advanced General Medicine—Harvard University Medical School,  
Courses for Graduates  
(3 weeks—March 31 to April 19, 1941)

Dr. Francis M. Rackemann, Director

- Course No. 5. Allergy—Massachusetts General Hospital  
(1½ weeks—April 10-18, 1941)

Dr. Chester S. Keefer, Director

- Course No. 6. Gastro-enterology—Boston University School of Medicine  
(1 week—April 7 to 12, 1941)

#### *Ann Arbor, Mich.*

Dr. Cyrus C. Sturgis, Director

- Course No. 7. General Medicine—University of Michigan Medical School and  
University Hospital  
(2 weeks—April 7 to 19, 1941)

Tufts College Medical School, Postgraduate Division  
Samuel Proger, M.D., Chairman  
30 Bennet St.  
Boston, Mass.

The courses announced below are designed for the general practitioner who wishes to bring his knowledge up to date. The work is largely given in the New England Medical Center. In addition to the tuition fees noted below, there is a \$5.00 registration fee which covers all courses taken within a twelve-month period.

*Internal Medicine*—Samuel Proger, M.D., in charge.  
January 6–February 1, 1941; fee, \$50.00.

*Advanced Electrocardiography*—Heinz Magendantz, M.D., in charge.  
January 6–8, 1941; fee, \$20.00.

*Dermatology B*—William P. Boardman, M.D., in charge.  
January 20–25, 1941; fee, \$25.00.

*Diabetes*—Joseph Rosenthal, M.D., in charge.  
January 20–25, 1941; fee, \$25.00.

*Endocrinology*—Charles H. Lawrence, M.D., in charge.  
February 3–8, 1941; fee, \$25.00.

*Recent Advances in Certain Fields of Internal Medicine*—Robert W. Buck, M.D., in charge.  
February 24–March 1, 1941; fee, \$25.00.

*Pediatrics*—  
March 3–29, 1941; director and fee not yet announced.

*Hematology A*—Heinrich G. Brugsch, M.D., and William Dameshek, M.D., in charge.  
March 3–8, 1941; fee, \$25.00.

*Gastro-enterology*—Katherine S. Andrews, M.D., in charge.  
March 17–22, 1941; fee, \$25.00.

*Rheumatic Diseases*—Heinrich G. Brugsch, M.D., in charge.  
March 24–29, 1941; fee, \$25.00.

*Allergy*—Ethan Allan Brown, M.D., in charge.  
April 7–12, 1941; fee, \$25.00.

*Electrocardiography*—Heinz Magendantz, M.D., in charge.  
April 14–19, 1941; fee, \$25.00.

*Cardiology*—Samuel Proger, M.D., in charge.  
April 21–26, 1941; fee, \$25.00.

*Internal Medicine*—Samuel Proger, M.D., in charge.  
April 28–May 24, 1941; fee, \$50.00.

*Dermatology A*—Francis M. Thurmon, M.D., in charge.  
May 12–17, 1941; fee, \$25.00.

*Endocrinology*—Charles H. Lawrence, M.D., in charge.  
May 19–24, 1941; fee, \$25.00.

*General Medicine*—Harry Linenthal, M.D., Hyman Morrison, M.D., and Associates.  
June 30–July 26, 1941; fee, \$50.00.

*Columbus, Ohio*

Dr. Charles A. Doan, Director

Course No. 8. Clinical Medicine from the Hematologic Viewpoint—Ohio State University College of Medicine

(1 week—April 14 to 19, 1941)

*Philadelphia, Pa.*

Dr. William D. Stroud, Director

Course No. 9. Cardiology—University of Pennsylvania School of Medicine and Graduate School of Medicine

(2 weeks—April 7 to 19, 1941)

*Washington, D. C.*

Dr. Wallace M. Yater, Coordinator

Course No. 10. Military Medicine—The Public Services of the United States

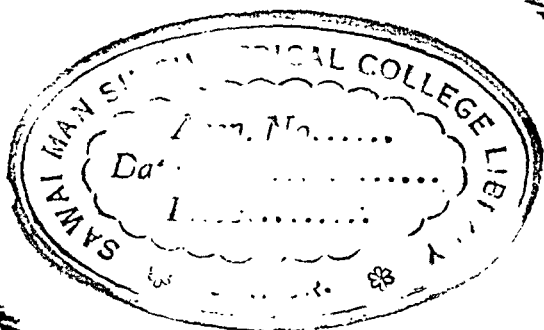
(2 weeks—April 7-18, 1941)

The two courses in Allergy have been correlated and essentially will cover the same subject matter. The course in General Medicine at the University of Michigan Medical School and the course in Hematology at the Ohio State University College of Medicine will be a repetition of the same courses given under the auspices of the College in the spring of 1940. The advanced course in General Medicine at Harvard University Medical School has been organized as a super-advanced course, covering a period of three weeks.

Because of the present world situation and the Preparedness Program of the United States, a course in Military Medicine will be given under the auspices of the U. S. Army Medical Corps, U. S. Navy Medical Corps and the U. S. Public Health Service in Washington. Experts on various medical phases of medical preparedness and military medicine will give the course, which will be of considerable value even to those internists who do not anticipate participation in military affairs.

A one week's course in Cardiology and a one week's course in Gastro-enterology have been scheduled in Boston on alternate weeks, giving members who desire an opportunity to take both courses.

Detailed bulletins of the courses have been distributed to all members of the College.



*Hematology C*—William Dameshek, M.D., in charge.

July 7-19, 1941; fee, \$75.00.

Detailed schedules of most of the above courses are available and will be sent upon request.

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#### FELLOWSHIPS

Through the Bingham Associates Fund, fellowships for postgraduate study are available for physicians practicing in Maine who are members of the Maine Medical Association. Application should be made to the Chairman. These fellowships are not available to physicians from other parts of New England; the tuition fees, however, are placed at a level calculated to make the courses available to the great body of physicians in New England.

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Tulane University of Louisiana School of Medicine  
Maxwell E. Lapham, M.D., Dean  
1430 Tulane Ave.  
New Orleans, La.

#### *Review Courses*

Review courses are designed largely for general practitioners, but offer a rather comprehensive review for anyone who has been unable to keep abreast of the literature.

*The Medical Review Course*—Jan. 6 to Feb. 1; Feb. 3 to March 1; March 3 to March 29, 1941.

In addition to medicine, includes pediatrics and some radiological interpretation. This course is repeated according to above dates. Fee, \$100.00.

Throughout the year Tulane University arranges on demand part-time intensive instruction in certain subjects such as cardiology, pediatrics, cystoscopy, etc.

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University of California Medical School  
M. S. Marshall, M.D., Acting Dean  
San Francisco, Calif.

*Clinical Aspects of Dermatology*—January 6-8, 1941.

Dr. S. R. Mettier, F.A.C.P., Associate Professor of Medicine, in charge. This short comprehensive course is designed to meet the needs of physicians engaged in private practice. Many of the discussions will be illustrated by patients, lantern slides or pathological material. Registration closes December 31, 1940. Fee, \$20.00.

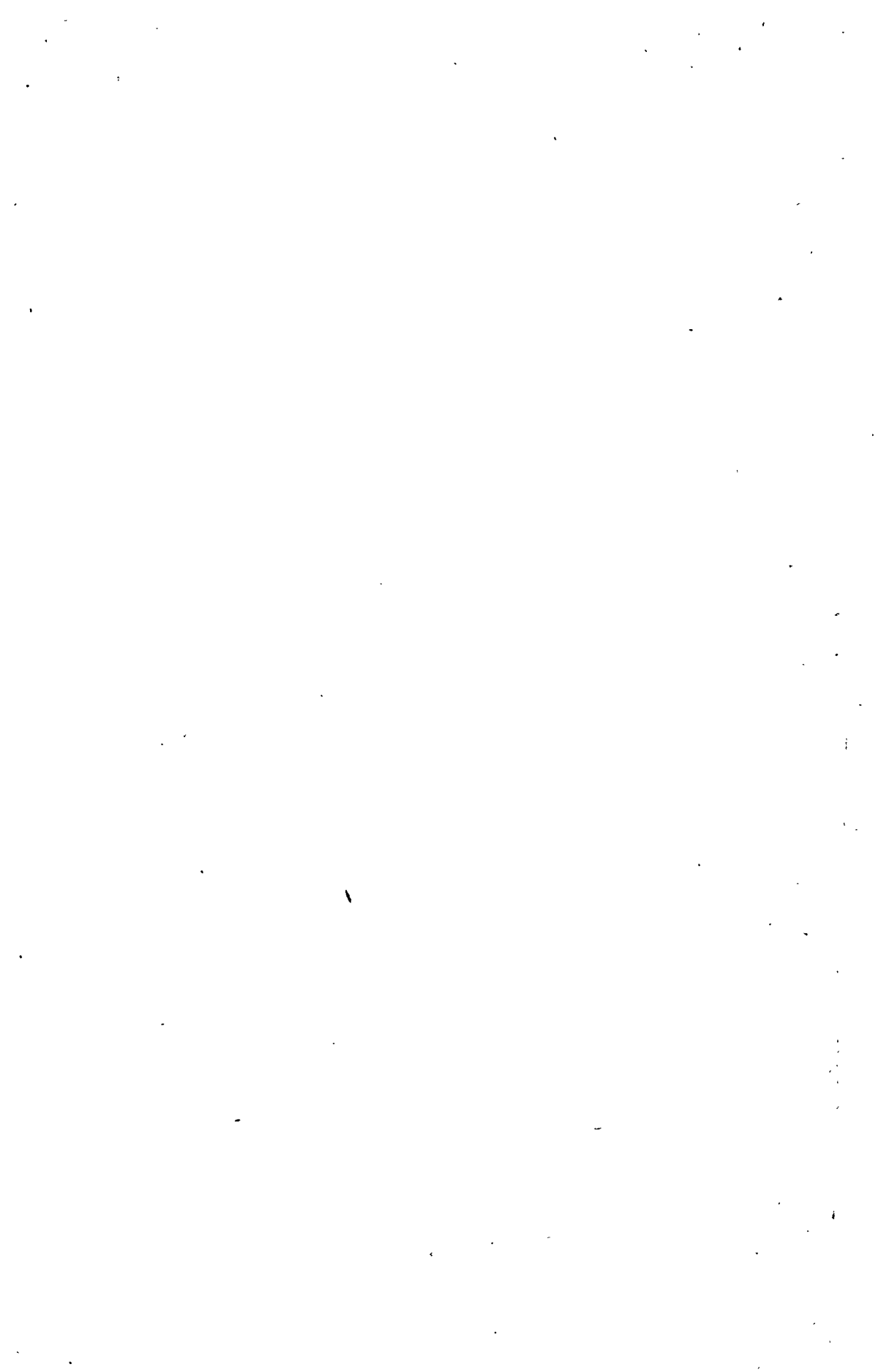
In June, 1941, another refresher course will be given, but subject and announcements referring thereto will come later.

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University of Chicago, Division of the Biological Sciences  
c/o Dean of Students, Biological Division  
Chicago, Ill.

#### *1. Advanced Gastroscopy*

Course given under supervision of Dr. Schindler; limited to one student per College quarter; course offered during the summer, autumn and winter quarters; fee, \$150.00.



## 2. *Gastroscopy*

Two weeks, repeated each month at definite periods; fee, \$100.00; course under direction of Dr. Schindler; registration limited to three physicians; applicants requested to indicate on their applications what special preparation or experience they have had in this field; arrangements for the course usually should be made many months in advance.

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University of Georgia School of Medicine  
G. Lombard Kelly, M.D., Dean  
Augusta, Ga.

By special arrangement with the Head of the Department of Medicine, the University of Georgia School of Medicine will receive for training a limited number of physicians who may desire postgraduate training in internal medicine. Arrangements for such training may be made with the Professor of Medicine.

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University of Illinois  
1853 W. Polk St.  
Chicago, Ill.

This institution offers no short intensive courses in internal medicine, but does offer graduate work leading to the Master's Degree in Medicine, based on research and advanced study; further details to be secured from the Recorder.

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University of Michigan Medical School  
A. C. Furstenberg, M.D., Dean  
Ann Arbor, Mich.

The Department of Postgraduate Medicine of the University of Michigan announces the following annual postgraduate courses for the spring of 1941:

### *Allergy*

Course in clinical phases of allergy offered to a limited group; taught mainly by demonstrations; includes study of asthma, hay fever, food allergy, eczema, contact dermatitis and dust sensitization, with methods of recognition and treatment. The practical aspects and office management of these conditions are emphasized. The course is arranged so that the entire field of allergy can be presented over a period of successive years. One week; fee, \$10.00.

### *Diseases of Blood and Blood-Forming Organs*

Course consists of a comprehensive review of the present knowledge of the blood, its physiology, embryology, and pathology. Clinical and laboratory studies are made of a selected group of patients. Standard laboratory methods are demonstrated and analyzed, and special features, as bone-marrow puncture, blood transfusion, etc., are considered. The course is planned to enable the physician to obtain a better understanding of the status of blood-forming organs and to select the most adequate treatment for his patients. One week; fee, \$7.50.

### *Diseases of the Heart*

Clinical aspects of heart disease are stressed in this short intensive course. Instruction includes examination of patients and practical demonstrations of cases. References for study in advance of the course are suggested. Three days; fee, \$5.00.

when climbing mountains. In May 1935, while travelling on the train, he felt a constricting cardiac pain, which radiated between the scapular regions and lasted for a quarter of an hour. Two months later a similar attack of pain occurred, coming on at night time, and lasting for several hours; a third attack of pain made its appearance two weeks later, and was followed by unconsciousness. The patient was brought to the hospital and a diagnosis of cardiac infarction was made. The recovery was very slow, and the patient was readmitted to the hospital three months later.

Clinical examination: During systole one could observe a definite systolic propulsion, most marked at the level of the fifth rib, between the left midclavicular and the left parasternal line (figure 1). This pulsation extended slightly beyond the left mid-

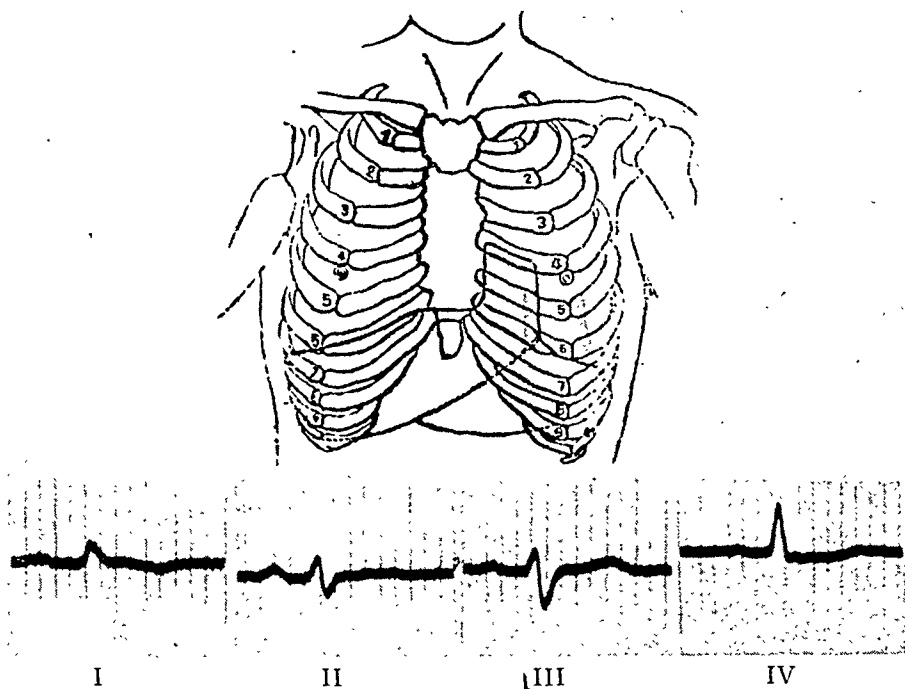


FIG. 1. Case 1. *Above:* Scheme of chest. The shadowed area indicates the extent of the precordial pulsation. *Below:* Electrocardiogram with the three limb-leads and the precordial lead (IV). In the latter the galvanometer connections are so made that relative negativity of the exploring electrode is represented by an upward deflection.

clavicular line and caudad to the sixth rib. The heart sounds were of low intensity, and no murmurs were heard. The heart rate was 64 per minute, and the rhythm was regular. Blood pressure varied between 95 mm. of mercury systolic with 95 diastolic and 80/50. Electrocardiographic findings (figure 1): Sinus rhythm was present, and the voltage in all leads was diminished; a well marked S deflection was noted in Leads II and III and a small R in Lead I. T in Lead I was slightly negative, and the R-T segment showed a slight elevation. In the chest lead\* the initial downward stroke was absent, and T was flat positive. Radiological study: No changes characteristic of cardiac aneurysm were noted. Orthodiagram (figure 2) revealed a moderate degree of cardiac enlargement, with the oblique diameter measuring 15.5 cm. The amplitude along the left lower contour, as observed fluoroscopically, was exceedingly small. The

\* The chest leads were taken in this and in the following cases from the apex region and the left leg; the right arm cable was connected with the precordium, the left foot cable with the left leg, so that relative negativity of the exploring electrode was represented by an upward deflection.

### *Electrocardiographic Diagnosis*

This course consists of lectures with lantern slides and demonstrations, and the examination under supervision of a large number of electrocardiograms from the files of the laboratory. One week; fee, \$25.00.

### *Nutritional and Endocrine Problems*

This course is planned to acquaint the practitioner with the fundamental principles of metabolism. The phenomenal advances in biological chemistry and clinical investigation have gone far to explain a number of disease conditions which either have not been understood or for which there was no satisfactory treatment. These conditions include diabetes mellitus, nephritis and edema, obesity, deficiency diseases, gout, and dysfunctions of the parathyroid and the adrenal glands. Material will be presented by means of lectures, demonstrations, and selected reading. One week; fee, \$7.50.

### *Pathology*

Four intensive courses, especially arranged for postgraduate students, are offered during the summer session. These courses are as follows:

*Special Pathology of Neoplasms:* Histopathological diagnosis of neoplasms with special emphasis on rare forms. Discussion on diagnosis, treatment, and prognosis. Laboratory open all day. Demonstration, 3-5 p.m. daily. Two weeks; fee, \$15.00.

*Pathology of the Female Genito-Urinary Organs:* This course deals with the microscopical pathology of the female genito-urinary tract, with special emphasis upon neoplasms of both external and internal genitalia. The more important infections are illustrated in their various situations and special attention is paid to the interpretation of endometrial curettings. Laboratory open all day. Demonstration, 3-5 p.m. daily. Two weeks; fee, \$15.00.

*Special Pathology of the Eye:* Laboratory open all day. Demonstration, 3-5 p.m. daily. Two weeks; fee, \$15.00.

*Special Pathology of the Ear, Nose, and Throat:* Laboratory open all day. Demonstration, 3-5 p.m. daily. Two weeks; fee, \$15.00.

### *Pediatrics*

This course, contributed by the American Academy of Pediatrics, consists of lectures and clinics on those conditions in infancy and childhood which contribute prominently to mortality and disability. Three days; no registration fee.

### *Diagnostic Roentgenology. III. The Skeletal System, Including the Skull*

This is the third in a series of courses in diagnostic roentgenology. This course will be limited in scope to roentgen consideration of the skeletal system including the skull. No instruction in roentgen technic will be offered. One week; fee, \$10.00.

*Internal Medicine*—Courses designed to prepare candidates for national specialty board examinations.

Courses are arranged in internal medicine and most of its subdivisions for indeterminate periods for those desiring special training. While exceptions may be made, these courses are primarily designed for those who have had the preliminary training required by the national specialty boards. Each course is arranged individually to take advantage of the large amount of pathological material, the anatomical and chemical laboratories, as well as the special departments in hematology, arthritis, serology and psychiatry. Fee, \$25.00 per month.

The program of this institution also calls for a number of postgraduate courses to be given during the summer of 1941, including courses in biological chemistry, dermatology and syphilology, internal medicine, clinical microscopy, neurology, pathology, autopsies, and medical roentgenology.



rest of the clinical examination was negative. The urine analysis revealed nothing abnormal, and the Wassermann reaction was negative.

On the basis of the peculiar precordial pulsation we diagnosed aneurysm of the heart, involving the ventral portion of the left ventricle. The patient was apparently making a slow recovery, when he died suddenly three weeks following admission. It so happened that two hours prior to death the area of pulsation had been mapped out carefully (figure 1), and after death a needle was perpendicularly introduced through the center of the former observed area of pulsations until it penetrated to the anterior heart wall. After removal of the anterior chest wall a drawing was made in situ (figure 3). It could be seen that the left ventricle bulged ventrally and participated much more in the formation of the anterior heart wall than is usually the case. The area of the propulsion, which had been observed on the chest wall during life, was marked on the drawing with a broken line, and it was noted that it fell entirely within the aneurysmal bulge. The point where the needle penetrated was visible just within the left ventricular margin; the apical portion was exclusively formed by the left ventricle and revealed a globular bulge the size of a fist. The wall of the left ventricle measured  $1\frac{1}{2}$  cm. at the level of the coronary sulcus; corresponding to the bulge, it measured only 2 mm. in thickness and consisted mainly of scar tissue. This bulge and thinning out affected a great part of the ventral and dorsal wall of the left ventricle as well as the lower portion of the interventricular septum. The inner contour of the aneurysm was coated with shallow thrombi partly organized. The microscopic examination showed the aneurysmal wall to consist of scar tissue in which it was impossible to distinguish any muscle tissue.

It has therefore been demonstrated that the pulsation of the chest wall, as observed during life, coincided with the aneurysmal pouch, which had been forced ventrad and laterad by the systolic increase in the intraventricular pressure.

*Case 2.* G. F., male, aged 42. At the age of 36 this patient had experienced typical anginal pain on effort, radiating to the throat and into both arms, which came on only after exertion and ceased upon rest. Two years later there was considerable aggravation, the attacks of pain occurring more often and also during complete rest. One year later there were two very severe attacks of pain, each lasting for several hours. Then dyspnea developed, so that the patient was hardly able to climb one flight of stairs. He was admitted to the hospital on August 8, 1932.

*Clinical findings:* A forceful cardiac thrust was felt, both with the patient standing and lying down. The systolic propulsion could be palpated between the lower margin of the fourth and the sixth ribs. It was about 6 cm. broad and extended from the left midclavicular line almost to the left parasternal line with a maximum in the fifth interspace in the left midclavicular line. The heart sounds were of very low intensity; murmurs were not present. The second sound was heard everywhere better than the first. The heart rate was 86 per minute, and the rhythm was regular. The blood pressure readings during the four years of observation varied between 150/80 and 85/60. *Electrocardiographic findings:* A deep Q deflection in Leads I and II was noted, and in Lead I, T was negative with the R-T segment slightly depressed. A precordial lead was not available at that time. *Radiological examination:* The heart was moderately enlarged; the oblique diameter measured 14.4 cm. The apical portion was plump. No abnormal intersection was noted along the silhouette contour. The right lower cardiac border was revealed as having an increased convexity. Normal findings were noted along the aorta. The amplitude of pulsations was normal at the base and very small near the apical pole. The circumference of the palpable area of pulsation was outlined by lead marks and fluoroscopy showed that the lower border of the pulsation was adjacent to the apical portion. The center of the pulsation was

University of Minnesota Medical School  
Dr. William A. O'Brien, Dean  
Department of Postgraduate Education  
Minneapolis, Minn.

This University maintains a Center for Continuation Study, which houses all postgraduate groups (as distinguished from undergraduate or graduate). Their courses in medicine are three to six days in length and are given in special or general fields. During the preceding autumn, six-day courses were given in clinical allergy, traumatic surgery, medical therapy in general practice, general surgery, obstetrics and proctology; also three-day courses in anesthesiology and in health problems of school children.

The Center contains living accommodations for seventy-eight persons, lounge, class rooms, garage, executive offices and dining room. It supplies complete living and learning service while the individual is present. The approximate cost for a six-day course in medicine is \$25.00 tuition and \$15.00 for complete living expenses. Mimeographed copies of all lectures are distributed. The staff includes not only that of the University plus that of the Mayo Foundation, but includes distinguished medical leaders from Minnesota and various medical centers of the country.

Among courses scheduled for the near future are: .

Problems of Executive Housekeepers—  
January 2-4, 1941.

Hospital Administration—  
January 27—February 1, 1941

Uterine Bleeding—  
February 3-5, 1941

Medical Social Service—  
February 13-15, 1941

Dietetics—  
February 20-22, 1941

Deficiency Diseases—  
March 3-5, 1941

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University of Virginia  
H. E. Jordan, M.D., Dean  
University, Va.

#### *Postgraduate Clinics*

During the session this University gives two postgraduate clinics, one in the autumn and one in the spring; these clinics are designed primarily for the practitioners of the State; specific dates not given; no registration fee.

#### *Recent Advances in Internal Medicine*

The above course was given June 17 to 22, 1940, and the intention has been expressed of giving the course again during June, 1941; fee, \$15.00.

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University of Wisconsin Medical School  
William S. Middleton, M.D., Dean  
Madison, Wis.

In addition to the opportunities in residencies and research fellowships, the University of Wisconsin Medical School has made the following announcement:

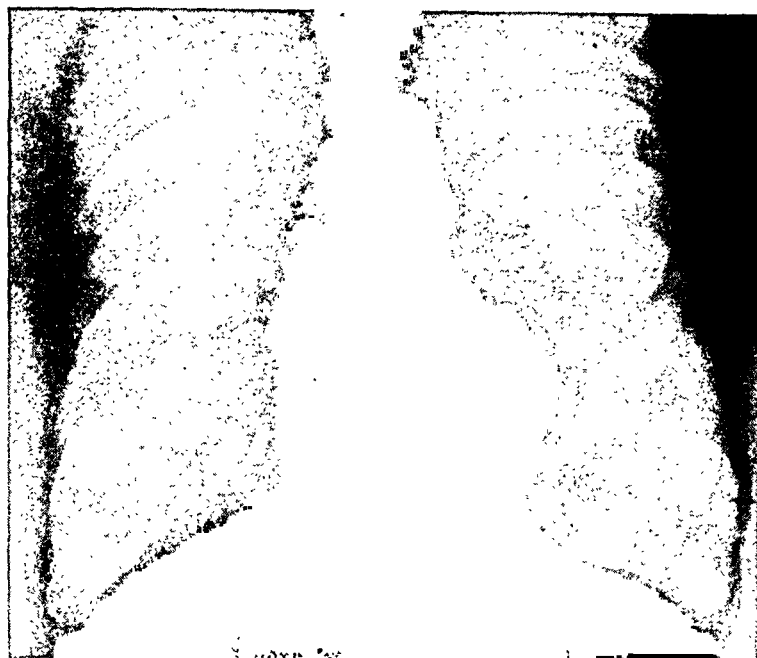


FIG. 4. Case 3. Roentgenogram: Anterior view showing a bulge along the left cardiac border.

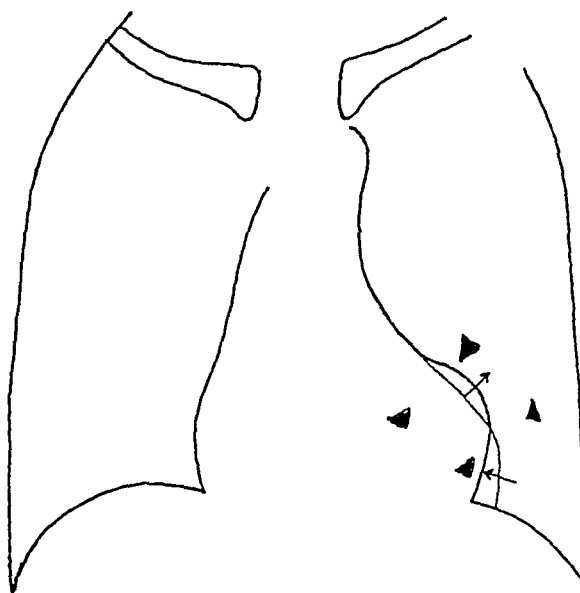


FIG. 5. Case 3. Orthodiagram showing the changes in shape along the left ventricular contour during systole, as indicated by arrows. The caudal part moves inward during systole, and simultaneously the cranial part is diverted outwardly. The limits of the area of the palpable precordial pulsation are indicated by lead marks. (This orthodiagram was made in expiration, whereas the roentgenogram (figure 4) was taken in deep inspiration.)

partial cardiac aneurysm by means of palpation, auscultation and percussion is generally and rightly considered to be impossible." Strandell<sup>7</sup> in 1930 likewise stressed the impossibility of detecting cardiac aneurysm by means of physical diagnosis, and stated: "As a rule one does not even think of it, when dealing with a case of heart disease."

One may rightly ask why so many very valuable observations in the field of physical diagnosis have been of so little avail in the diagnosis of the condition. The answer is that one important premise for the diagnosis was missing as yet; namely, clinical knowledge of cardiac infarction, which knowledge has been available only during the last 15 years. More recently the question has been approached again by radiologists and clinicians, and considerable progress has been made in the diagnosis of cardiac aneurysm. This has been the result mainly of proper physical examination, and only to a lesser degree of radiological examination. It is true that the radiologist has in some cases revealed definite findings which have been reliable signs for the presence of an aneurysm. We refer to a well defined bulge along the left border of the cardiac silhouette, sometimes associated with a systolic lateral pulsation over this area. A number of cases are available in which a diagnosis was thus established.<sup>8, 9, 10, 11, 12, 13, 14, 15</sup> On the other hand, those who have been interested in this subject have come to realize that characteristic radiological changes are often missed in the presence of aneurysm of the left ventricle. The reason for this will be discussed later.

The value of physical signs for recognition of cardiac aneurysm has been stressed increasingly, and palpable pulsatory phenomena of the chest wall have taken a prominent place. Great importance was attributed by Libman and Sacks<sup>16</sup> to the association of a feeble first sound and a pulsation most marked between the apex of the heart and the sternum. East<sup>8</sup> described two cases of cardiac aneurysm in which a diagnosis was made principally through the observation of a "wavy pulsation" above and inside the left nipple. The diagnosis was corroborated by the radiological study. Erlsbacher and Scherf<sup>17</sup> likewise reported on pulsatory findings which enabled them to diagnose cardiac aneurysm in three cases. These writers stressed the importance of an early retrogression of the pulsation, which had appeared within a few days following the coronary artery occlusion and had receded, in two cases, several weeks later when a firm scar had displaced the necrotic heart muscle tissue.

We have studied the clinical symptomatology of cardiac aneurysm mainly on the basis of pulsatory phenomena, and have been able to diagnose 10 cases during life in the course of the last four years. In the following report we want to outline the signs which have proved useful for the recognition of this important and not infrequent cardiac lesion.

#### CASE REPORTS

*Case 1.* H. F., male, aged 64. For the preceding five years the patient had experienced painful oppression in the cardiac region and respiratory effort limitation

pulsation corresponded exactly to the bulge visible along the margin of the left ventricle.

Since the second attack of anginal pain in 1934 the physical condition of the patient has been exceptionally good, as shown by the fact that he can walk at a quick pace for an hour at a time and has been walking up and down four flights of stairs from four to six times daily without any distress. Running upstairs, however, brings on precordial oppression.

*Case 5.* P. W., male, aged 45. In January 1932 the patient experienced while walking a constricting pain over the cardiac area, which lasted for a few minutes. A few days later he had a very severe attack of pain associated with perspiration, which lasted for 26 hours, radiating into both arms and necessitating injection with morphine. A febrile reaction followed. Subsequently the patient stayed in bed for 10 days only.



FIG. 6. Case 4. Roentgenogram, anterior view: The silhouette is considerably enlarged to the left, and along the upper ventricular contour a sudden change in direction is noted.

**Clinical findings:** Over a large precordial area a very forceful pulsation was noted, lifting not only the soft tissues but also the ribs. The maximum was at the level of the fifth rib, but the pulsation extended upward to the fourth, and downward to the sixth rib. This thrust reached unusually far medially—as far as to the left sternal border—and it was also felt 1 cm. outside the midclavicular line. It was most marked between the left parasternal and midclavicular line. The intensity of the heart sounds was low and there were no murmurs. The heart rate was 84, and the rhythm was regular. The blood pressure was 95/70. During the whole period of observation the systolic pressure never exceeded 115 mm. Hg. Electrocardiographic findings: Sinus rhythm, left axis deviation; a Q-wave was well developed in Leads I and II. In Lead I the R-T segment showed a minimal depression and  $T_1$  was negative. In the chest lead the initial downward stroke was absent and T was inverted and very tall.

In view of the history and the electrocardiographic changes, both of which indicated coronary artery occlusion, it was felt that the forceful precordial pulsation should be interpreted as indicating an aneurysm affecting the ventral wall and apical portion of the left ventricle. From the particular location of the pulsation it was con-

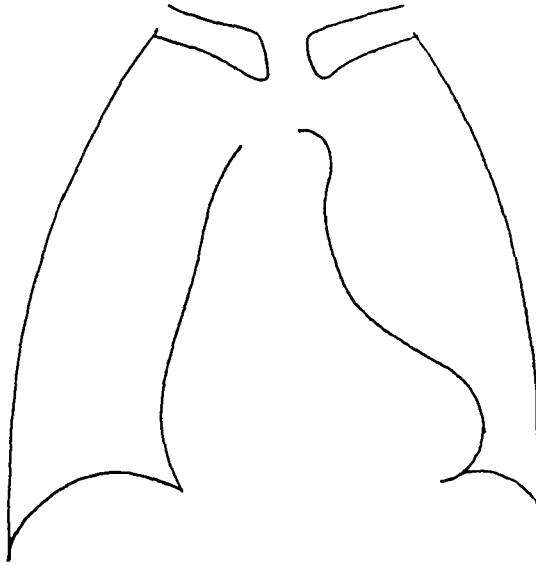


FIG. 2. Case 1. Orthodiagram indicating some widening, corresponding to the lower portion of the left ventricle. No circumscribed bulge is visible.

Aorta ↓

↓ Pulmon. A.

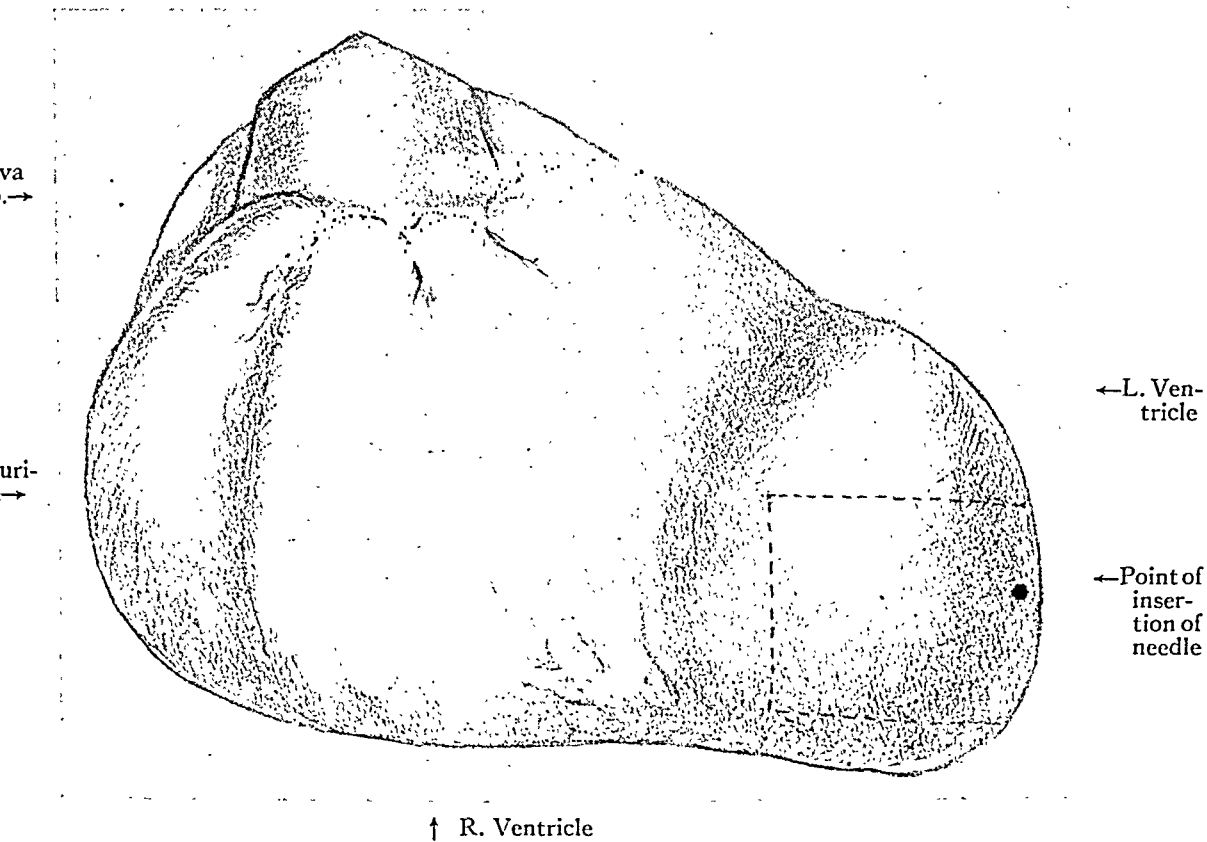


FIG. 3. Case 1. Drawing of the heart in situ. Note the large bulge along the ventral portion of the left ventricle. The broken line indicates the corresponding area of pulsation as it was noted during life.

area, particularly while leaning against a desk. In the years following the first attack of pain he had practiced skiing, and he was able to climb to an altitude of 6,000 feet without any real discomfort and could hike for 10 hours a day. Six years following the coronary artery occlusion his physical condition was quite satisfactory and he was able to undergo considerable exertion.

The next case is the only one in the series in which a diagnosis of cardiac aneurysm was made exclusively on the basis of radiological findings.

*Case 6.* H. C., male, aged 60. This patient had had two severe and prolonged attacks of anginal pain. In October 1929 he was seized by a severe attack of pain of retrosternal location, and this was accompanied by much perspiration. The patient was kept in bed for four weeks and then resumed light work, but on walking he experienced chest pain. An orthodiagram was taken at that time and showed a moderate degree of enlargement to the left, but no changes indicative of cardiac aneurysm. Another attack of chest pain very severe in nature occurred three and a half years later. This pain lasted throughout the night and required three hypodermic injections. At this time the patient stayed in bed for five days. He never has had similar attacks of pain since. Three months later, in 1933, the patient came under our observation.

**Clinical findings:** It required the most meticulous examination in order to detect pulsatory phenomena over the cardiac area. There was one pulsation in the left anterior axillary line at the level of the sixth intercostal space that was moderately strong in character and confined to an area 3 cm. in width. In addition one observed a rather weak and diffuse pulsation in an area between the sternum and the left parasternal line, covering the fourth and fifth interspaces. The apical sounds were of low intensity and almost inaudible over the base. The heart rate was 90, and the rhythm was regular. Blood pressure was 105/60, and during the course of the next four years arose to 150/90. The chest of the patient showed a considerable degree of emphysema, kyphosis, and a depression of the lower portion of the sternum. The rest of the examination revealed nothing of particular significance. Nothing abnormal was found in the urine, and the Wassermann reaction was negative. **Electrocardiographic findings:** A deep Q-wave was present in Leads II and III; a negative T deflection in all conventional leads. It was, therefore, probable that in addition to the posterior site the anterior heart wall had shared in the infarction.

**Radiological examination:** The roentgenogram (figure 8) showed the whole heart enlarged, more to the left but also to the right. The left ventricular contour revealed a large half-spherical bulge, which took off from the upper portion of the ventricle at a sharp angle. When the patient was turned slightly into the left anterior oblique view, the bulge was observed to extend dorsad, while in the left lateral view the bulge appeared as a nuclear dense shadow within the cardiac silhouette. Examination of the barium-filled esophagus revealed an impression from in front at the level of its lower third. This impression coincided with the top portion of the aneurysm, but obviously was not caused directly by this aneurysm, for it was not this but rather the left atrium which must have been adjacent to the esophagus. In the right anterior oblique view this esophageal impression and deviation could be clearly demonstrated, but the nuclear shadow caused by the aneurysm was less distinctly visualized in this view. Fluoroscopy showed a systolic lateral pulsation along the aneurysmal bulge, particularly along its upper portion, while the adjoining part of the uppermost left ventricular margin revealed the normal inward movement.

Subsequent to the second attack of coronary occlusion, the patient was invalided for several weeks. He then gradually recovered and was able to walk slowly for from two to three hours without distress. Chest pain was experienced only when walking rapidly. Later he was knocked down by a bicycle and suffered a fracture of the skull and cerebral contusion. From that time greater distress was experienced.

approximately 3 cm. above the apex region while the uppermost limit of the pulsating area was nearly 7 cm. distant from the apical portion.

The rest of the clinical examination was essentially negative. The urine revealed nothing abnormal, and the Wassermann reaction was negative. The patient improved, but steadily complained of effort-dyspnea and anginal pain. However, he was capable of working almost all the time as a cook. The blood pressure was low, with a systolic pressure usually below 100 mm. Hg. There was no change in the intensity and in the extension of the chest wall pulsations. Small amounts of digitalis and vasodilating drugs were beneficial. Four years later the patient died suddenly. On the basis of the peculiar precordial pulsation our diagnosis was cardiac aneurysm subsequent to coronary thrombosis affecting the ventral wall and apical portion of the left ventricle.

Postmortem findings: Over a localized area the pericardium was adherent to the ventral wall of the left ventricle. The heart was enlarged, the myocardium was grayish-red and pale in the inner layers. Over the lower anterior portion of the left ventricle, including the adjacent portions of the interventricular septum, there was a circumscribed saccular bulge, the wall of which showed extensive fibrosis and many grayish-whitish fibrotic areas on section. Both coronary arteries revealed a stenosing calcareous degeneration, and their lumen was almost occluded. The valves were normal.

In the next two cases to be reported the diagnosis of cardiac aneurysm was made on the basis of the characteristic palpable pulsation and was confirmed by radiological study.

*Case 3.* L. K., male, aged 68. This patient's condition started out in May 1933 with anginal pain which radiated into the left shoulder. Seven months later he had a very severe attack of pain in the cardiac area, with radiation into the left arm, lasting for 24 hours. He stayed in bed for two days only and then resumed his activities. Eight days later he experienced an even more severe attack, which was followed by unconsciousness. Fever developed and the patient stayed in bed for three months. A few months later, in April 1934, he came under our observation.

Clinical findings: With the patient standing one could notice a powerful systolic cardiac thrust with its maximum in the fifth intercostal space 4 cm. lateral to the left midclavicular line. The pulsation extended 3 cm. medial to the left midclavicular line. It could be palpated between the fourth and sixth ribs and was less distinct in dorsal decubitus. The apical sounds were of low intensity and hardly audible over the base. The heart rate was 52, and the rhythm was regular. The blood pressure was 115/65. Electrocardiographic findings: During four years of observation frequent alternation of sinus rhythm and middle nodal rhythm was noted. There were persistently present signs of cardiac infarction, namely, a deep Q and an inverted T in Leads II and III. With the exception of a moderate degree of pulmonary emphysema the rest of the examination was negative. Nothing abnormal was found in the urine, and the Wassermann reaction was negative.

The findings as to the chest wall pulsations, in connection with the history, caused us to diagnose cardiac aneurysm. The radiological study corroborated the clinical diagnosis. The roentgenogram (figure 4) revealed a bulge protruding at the middle of the left cardiac border. This was particularly well noted during fluoroscopy with the patient slightly turned into the left anterior oblique position, and this because of the extension of the aneurysm dorsad. The following observations as to the pulsations were made during fluoroscopy and indicated on the orthodiagraphic drawing (figure 5). During diastole the left ventricular contour appeared to be nearly normal; during systole, however, a bizarre shape appeared; the lower half of the contour revealed a normal inward movement while the upper half bulged outward. It was concluded that the lower portion of the ventricular wall had still sufficient muscular tissue



Leads II and III. The initial downward stroke in the chest lead was absent. R-T segment in Lead I was slightly elevated, and T was negative. In Leads II and III, T was positive. In the chest lead the R-T segment was lowered and T positive.

On the basis of the abnormal pulsations, together with the patient's history and electrocardiographic alterations, a diagnosis of cardiac aneurysm was established. Radiologic examination (figure 9): The heart was distinctly enlarged to the left, and at about the middle of the left contour there was clearly noted a half-spherical bulge, which did not reveal an abnormal pulsation.

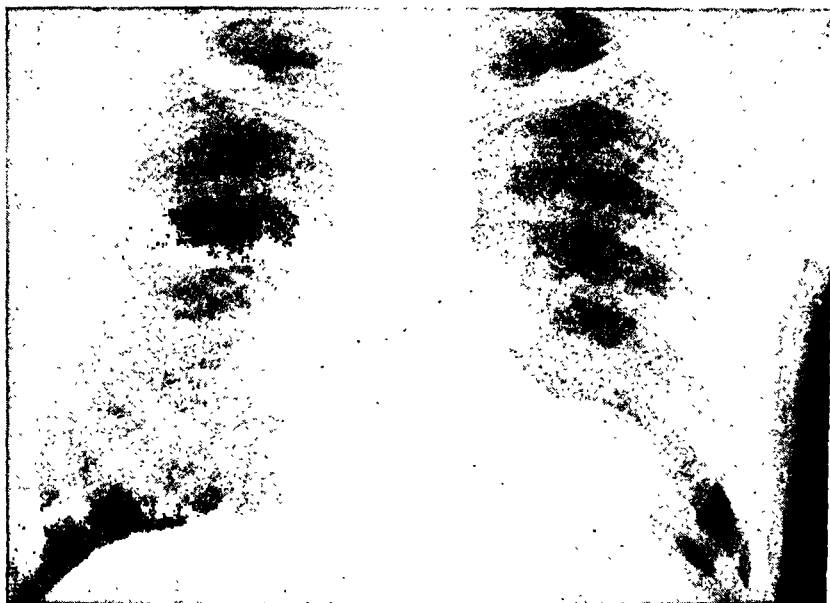


FIG. 9. Case 7. Roentgenogram, anterior view. The cardiac shadow is enlarged to the left and a half-spherical bulge is noted at the middle of the left ventricular contour.

*Case 8.* T. M., male, aged 59. In September 1934 the patient experienced a slight pain in the center of the chest, which responded to analgesic medication. One week later an attack of severe pain was experienced radiating into the left arm and lasting, with short remissions, for a period of three days. The patient was kept in bed for six weeks. From that time increased sensitivity to cold was noted, causing an unpleasant sensation in the cardiac area. A few months later there occurred severe attacks of cardiac asthma and pulmonary edema. At this time the patient came under our observation.

**Clinical findings:** Over a wide precordial area a pulsation was felt which forcefully lifted the soft tissues and ribs during systole. It was most marked in the fifth interspace in the midclavicular line, affecting also the fifth and sixth ribs. Laterally the thrust extended 2 cm. beyond the left midclavicular line, and medially it reached the left parasternal line, its total width measuring 9.5 cm. The character of the pulsation was hardly different from the one observed in the presence of left ventricular hypertrophy. The heart sounds were dull and of low intensity. Heart rate was 76; and the rhythm was regular. Blood pressure was 120/65. The rest of the examination was essentially negative. Nothing abnormal was found in the urine; the Wassermann reaction was negative. **Electrocardiographic findings:** A well marked Q deflection was noted in Lead I, and a *deep S* in Leads II and III, while in the chest lead the initial downward stroke was absent. The R-T segment in Lead I was slightly elevated, and T was negative. The S-T segment in Leads II and III was isoelectric,

left to contract normally, resulting in a normal centripetal systolic movement, while the superior portion was attenuated and almost wholly transformed into scar tissue, so that it was forced outward by the high systolic intraventricular pressure. As an additional study the region of the palpable pulsation on the chest was marked by means of lead marks. The subsequent fluoroscopic examination showed (figure 5) the area of pulsation to correspond almost exactly to the upper ventricular portion. A roentgenogram taken in right anterior oblique view showed the barium filled esophagus to deviate slightly dorsad at the level of its lower third.

This patient has been observed over a period of four years, and he has been able to walk for half an hour at a time without distress. Ascending one flight of stairs, however, causes some dyspnea and chest pain. It is worth reporting that one year and a half after the coronary occlusion a gastrectomy was performed on this patient without any untoward cardiac complications.

*Case 4.* S. S., male, aged 46. At the age of 39, while watching a football match, he suddenly experienced severe oppression in his chest, lost consciousness and was brought to a hospital. Here a diagnosis of sunstroke was made, and the patient was discharged three days later on his request. He continued to work for eight days, but felt very ill and had another attack of unconsciousness; he was sent to a hospital again, where he stayed for 17 days. Because of cough he was rehospitalized two weeks later, on which occasion a diagnosis of cardiac aneurysm was made. Subsequently the patient felt all right and was able to walk for one hour straight without complaints. Carrying loads, however, would bring on pressure in his chest. Four years after the first attack the patient suffered another attack of severe anginal pain. A year later he came under our observation.

*Clinical findings:* There was present a very forceful, broad and resistant cardiac thrust distinctly felt in the fifth intercostal space and extending 3.5 cm. to either side of the midclavicular line. The quality of the pulsation was quite similar to the thrust noted in the presence of left ventricular hypertrophy, and the impulse was so forceful that during systole the entire lower half of the chest shifted jerkily from right to left, with even those parts of the chest below the sixth rib showing some pulsatory movement. The heart sounds were of very low intensity. Murmurs were not present. The heart rate was 72 per minute, and the rhythm was regular. The blood pressure was 110/65. Electrocardiographic findings: Low voltage was present in the limb leads. In Lead I, Q was well marked, R small, and the R-T segment was slightly elevated; a rather deep S deflection was present on Leads II and III. In the chest lead the normal initial downward stroke was practically absent. The rest of the clinical examination was essentially negative. Nothing abnormal was found in the urine, and the Wassermann reaction was negative.

The diagnosis of cardiac aneurysm was established on the basis of the history and of the pulsatory chest wall movements.

*Radiological examination:* The roentgenogram (figure 6) showed a marked enlargement to the left with the oblique diameter measuring 17 cm. At the upper third of the left contour there was noted an abrupt directional change below which a globular bulge appeared. During fluoroscopy this latter area showed clearly a systolic distention, while the adjacent cranial portion of the ventricular contour revealed a normal inward movement. A roentgenogram made two years later showed that calcium deposits had developed along the bulging part of the silhouette. The radiologic findings indicated that the aneurysmal enlargement affected not only the apical region but extended far cranial, involving the ventral and lateral walls of the left ventricle. A film taken in the right anterior oblique view showed a very slight impression on the lower third of the barium-filled esophagus. The aneurysmal bulge could be visualized ventrally (figure 7). By mapping out the area of chest wall pulsation by means of lead marks, we were able to demonstrate during fluoroscopy that the area of palpable

right arm, lasting for two to three minutes. In December 1935 the patient experienced an attack of severe pain, starting in the right arm and spreading to the central portion of the chest and to the left arm, accompanied by perspiration. This lasted from noon until evening, but a chest pain of lesser severity was felt for several days longer. There was also a slight rise in temperature. The patient was in bed 10 days and then resumed work. He was seen on the twelfth day following the attack. Examination of the patient while standing revealed a barely palpable "apical thrust" in the fourth interspace in the left midclavicular line; high position of the diaphragm was also noted. The heart sounds were of low intensity and clear. Blood pressure was 125/90. Strict bed-rest was ordered. Reëxamination four weeks later revealed a large forceful pulsation corresponding to the place of the former "apical thrust." This propulsion extended from the third interspace to the fifth rib and its width was 7.5 cm. The larger part of the pulsation, 5 cm. in width, was outside of the midclavicular line. The smaller part, 2.5 cm. in width, was inside. The maximum of pulsation was in the

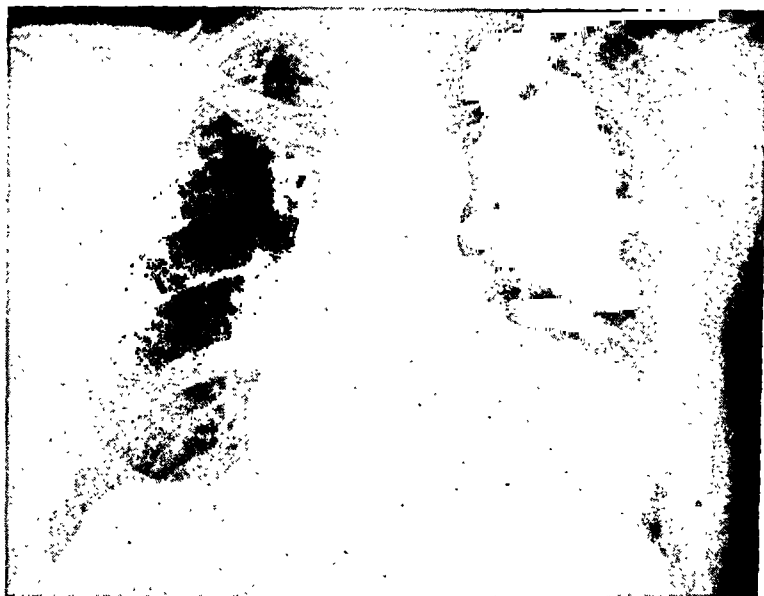


FIG. 10. Case 10. Roentgenogram, anterior view. The heart is considerably enlarged to the left, and the left lower portion of the silhouette bulges. Note the kinking at the cranial aspect of the left ventricular contour.

fourth interspace outside of the midclavicular line. Upon palpation of the propulsion, the patient stated that he felt "a tension" over this area and much more so when standing as compared with lying down. Electrocardiographic findings: Low voltage was present in all leads. The initial deflection in Lead I showed a deep Q, and the initial downstroke in the chest lead was absent. The R-T segment in Lead I was slightly elevated, and T was deep negative. In Lead III the T-wave was abnormally tall. The S-T segment in the chest lead was depressed, and T was positive.

Radiologic examination: On the occasion of the first examination, which was 12 days after the onset of the attack of severe pain, the heart was found to be in transverse position, moderately enlarged to the left, with an oblique diameter of 14 cm. Upon reëxamination six weeks later the heart was much larger and the oblique diameter measured 17 cm. (figure 10). The left ventricular contour revealed a large half-spherical bulge which took off near the base in the form of an angular kink. Along the bulge one could note during fluoroscopy a systolic lateral movement of small amplitude. In the right anterior oblique view the barium-filled esophagus was

cluded that the aneurysmal bulge affected the medial portion of the anterior wall of the left ventricle rather than the lateral portions. Radiologic examination: It was not surprising to find that there was no characteristic change along the cardiac silhouette, indicating a ventricular aneurysm. There was noted a moderate enlargement of both sides; the oblique diameter measured slightly less than 14 cm. There was no undue bulge along the cardiac contour, no sign of left ventricular hypertrophy. Fluoroscopy

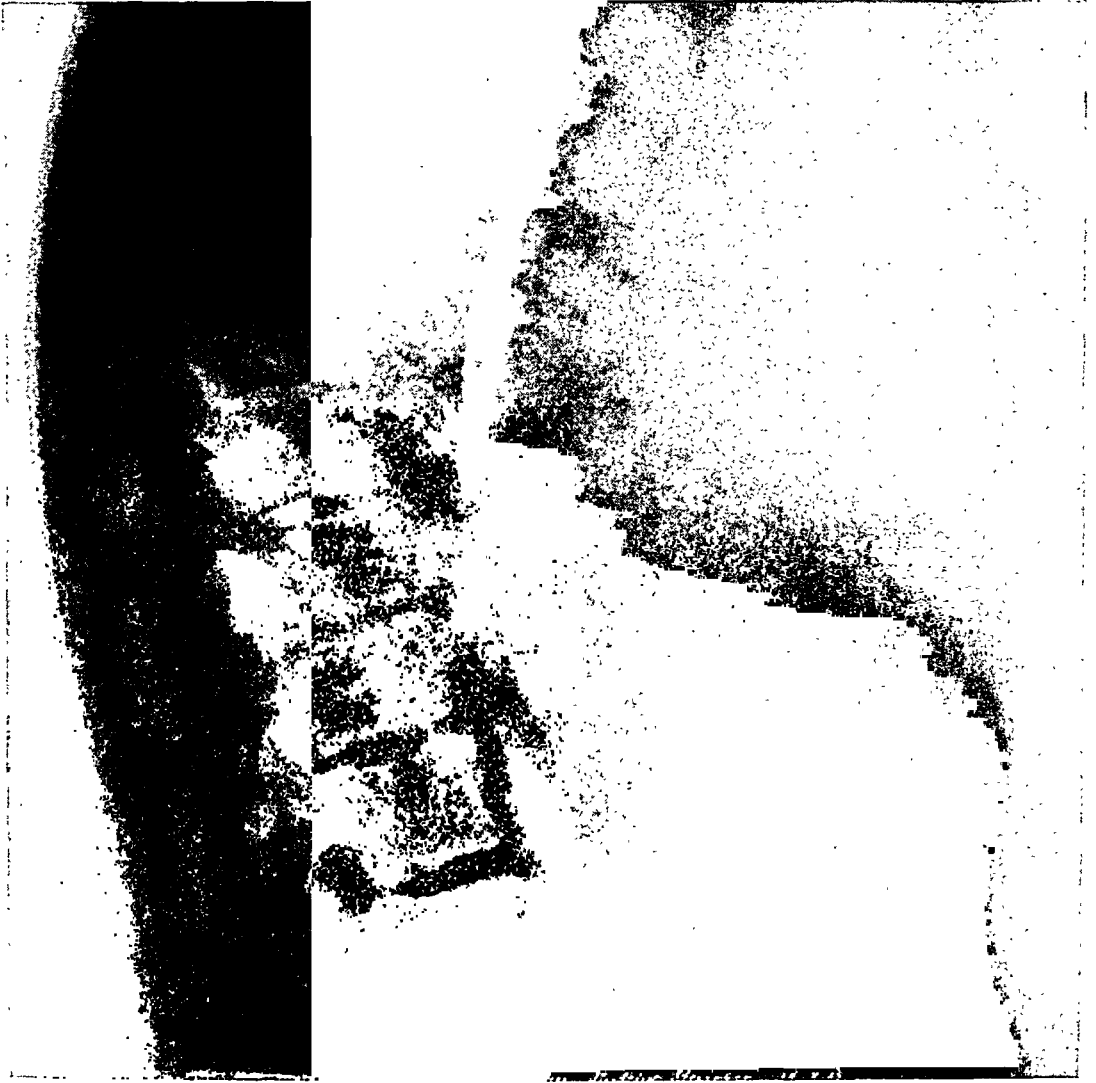


FIG. 7. Case 4. Roentgenogram, right anterior oblique view: High degree of rotation. The aneurysmal bulge is noted ventrally.

revealed a normal systolic inward movement along the left ventricular margin, and it was therefore assumed that a sufficient amount of active muscular tissue was still present. The rest of the clinical examination was negative. Examination of the urine revealed nothing abnormal, and the Wassermann reaction was negative.

This patient was capable of a remarkable degree of physical capacity in spite of serious heart disease. While walking he seldom experienced precordial oppression. He was, however, often disturbed by a sensation of forceful pulsation in the cardiac

jority of cases we found the maximum pulsation at the level of the fifth rib, in the neighborhood of the left midclavicular line. The characteristic pulsation is not of that circumscribed type which is often present in cases of hypertrophy of the left ventricle, but is rather a diffuse, large cardiac thrust; it extends not only over several intercostal spaces but is remarkable for its width, which often measures from 7 to 9 cm. In cases where the radiological examination reveals a bulge along the left ventricular margin, the pulsation may extend considerably beyond the left midclavicular line. Sometimes, however, the maximum pulsation is found inside the midclavicular line, and extends considerably medially. This is found in cases where the aneurysmatic distention apparently affects the parts of the anterior ventricular wall near the septum and where the radiogram reveals but little widening of the left ventricular margin.

The palpable pulsation is generally quite forceful and its resistance is certainly not less than that of the powerful pulsation caused by a hypertrophic left ventricle. Sometimes it is actually not possible to distinguish clearly between hypertrophy of the left ventricle and cardiac aneurysm. It is rather the diffuse character of the cardiac thrust, its localization above the fifth intercostal space, and its considerable extent towards the sternum that are indications of the existence of a cardiac aneurysm. In each case it is recommended that all those factors be excluded which might be causative of left ventricular hypertrophy. The history and electrocardiographic findings of preceding cardiac infarction are valuable supporting evidence. Sometimes one is able to watch the development of a precordial pulsation following coronary artery occlusion, and this supports the diagnosis. The pulsation may be noted within a few days following the attack of pain, and quickly develops its permanent character. If once established, no further changes in the pulsatory phenomena due to cardiac aneurysm were noted in our cases during the subsequent years. Occasionally a pulsation may undergo regression a few weeks after its appearance.<sup>17</sup>

If the radiological examination reveals characteristic alterations, these are without doubt the most definite and trustworthy signs of a cardiac aneurysm. There may be a circumscribed bulge along the margin of the left ventricle, usually at the level of the middle or upper portion of the left cardiac contour and an abrupt change in the course of the left cardiac margin, as a rule seen near the base. One can often recognize the aneurysmal nature of a bulge by a systolic lateral pulsation, which contrasts sharply with the normally directed centripetal movement of the adjacent, intact muscular portions of the ventricle. Obviously we must not confine ourselves to the study of the roentgenogram, but must also subject the patient to a very careful fluoroscopic examination; it is then not unusual to find a very slight bulge which was not noted in the roentgenogram, while the observation of a systolic lateral pulsation proves the existence of a cardiac aneurysm at this level. For the proper timing of such pulsations it suffices to compare the pulsation observed with the radial pulse. Occasionally the bulge in the anterior wall

Chest pain occurred even during rest, and at times Cheyne-Stokes breathing was present.

*Case 7.* R. R., male, aged 53. Without preceding anginal pain he experienced in November 1936 "heart burn" in the middle of the chest, lasting for a couple of hours without any radiation. According to his account, the discomfort had been only slight, but this statement was perhaps not reliable because it was learned that morphine had been injected for relief. The patient was kept in bed for eight weeks. The pain did not recur, and the patient complained bitterly that he was urged to avoid any

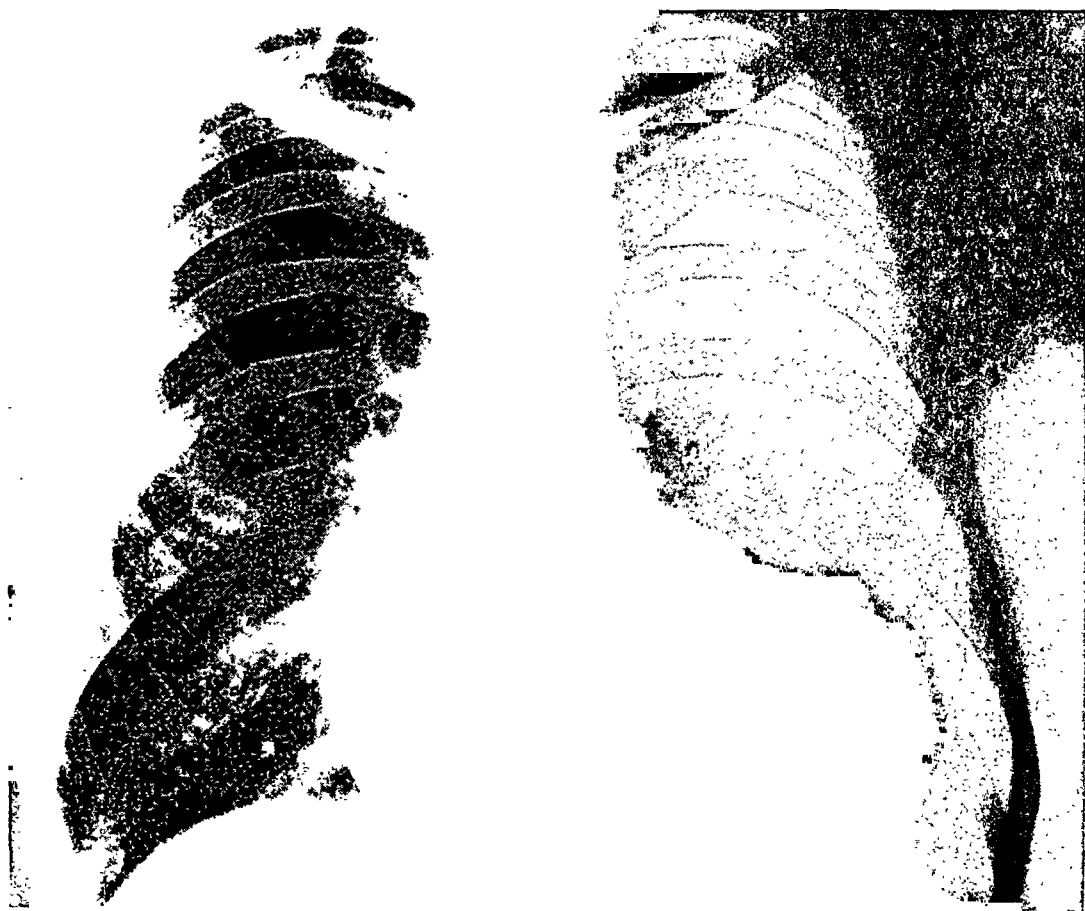


FIG. 8. Case 6. Roentgenogram, anterior view: The silhouette is enlarged to the right and to a greater degree to the left. Note how the left upper cardiac contour changes suddenly in direction where it meets the outline of the bulge.

physical effort in spite of his feeling perfectly well. He was first examined by one of us five months following the attack.

Clinical findings: A forceful systolic thrust was noted in the fourth and fifth intercostal spaces, particularly at the level of the fifth rib and extending from the left parasternal line to a point some 2.5 cm. beyond the midclavicular line. This pulsation could be felt better with the patient standing. The heart sounds were distant, just audible over the apical area but almost inaudible over the base. The heart rate was 84 and the rhythm was regular. Blood pressure was 110/80. The rest of the examination was entirely negative. Nothing abnormal was found in the urine, and the Wassermann reaction was negative. Electrocardiographic findings: In Lead I a Q wave was present, and the voltage of R was small. There was a deep S deflection in

region. These cases are rather rare. By far the larger number of cases of cardiac aneurysm are situated in the apical area, and in the nearby regions of the anterior wall of the left ventricle, and of the septum. These aneurysms of apical location are buried in the left hepatic lobe, making for themselves a bed in this organ, and they appear by radiological examination as an uncharacteristic elongation of the apical portion of the left ventricle.<sup>2</sup>

The diagnosis of cardiac aneurysm is much enhanced by finding evidence of a preceding cardiac infarction. Hence, in addition to a good history, electrocardiographic alterations are of great significance. Actually, in none of our 10 cases were electrocardiographic signs for cardiac infarction missing; and this included instances of many years' duration. Eight cases revealed the characteristic features of the anterolateral location, while two showed evidence for postero-diaphragmatic site. The dorsal extension of the aneurysm in these two cases could be demonstrated by the radiological examination. In one of them, with a history of two attacks of pain, there was electrocardiographic evidence for both anterior and posterior location. In half of our cases there was noted a deep S deflection in Leads II and III, and this included cases where there were no findings indicative of left sided hypertrophy. The electrocardiographic changes once developed appeared to be very constant in our cases of cardiac aneurysm.

All of the cases which we have observed have occurred in males. This is not remarkable in view of the fact that sclerosis of the coronary arteries, without associated hypertension, shows a definite prevalence in the male sex. The age at which coronary artery occlusion occurred varied in our patients between 39 and 64 years. Four cases occurred in early middle-life (39, 39, 40, 43 years, respectively).

It is noteworthy that one half of our cases have suffered two or even three severe anginal attacks of long duration. In three cases the attack was accompanied by loss of consciousness. Mention should be made of the significant fact that out of our 10 cases, only two had had complete and prolonged bed rest. In the eight remaining cases rest in bed was limited to a few days only, for the simple reason that the nature of the disease was not recognized at that time. The knowledge of this fact should possibly prove of significance in an attempt to prevent the formation of a cardiac aneurysm. Adherence to the prescribed régime of strict and prolonged bed rest, however, will not provide absolute protection, as is demonstrated by one of our cases. This patient had adhered strictly to a régime of rest from the very beginning of the disease.

Our final remarks concern the prognosis of cardiac aneurysm, the question of the expectation of life and of physical capacity of those afflicted with the disease. We are well aware that the validity of the following conclusions is limited since our study has been based solely upon those cases which have been recognized during life and have been under our observation for periods up to four years; cases which were not discovered until autopsy were not taken into consideration. Out of our 10 cases, sudden

and T positive. The S-T segment in the chest lead was much lowered, and T was isoelectric.

The referring physician reported that prior to the attack of pain there had been no elevation of the blood pressure.

The findings of abnormal pulsations in the precordial area, together with the history and the electrocardiographic alterations, indicative of cardiac infarction, led to the diagnosis of cardiac aneurysm affecting the ventral wall and apical portion of the left ventricle.

**Radiologic examination:** The cardiac silhouette was enlarged, particularly to the left, the oblique diameter measuring 17 cm. No abnormal bulge was noted. The area of the palpable cardiac thrust was indicated by lead marks, and subsequent fluoroscopy revealed the amplitude of pulsations at this level quite small. A follow-up study three years after the attack of pain revealed that the patient experienced slight dyspnea, but was well otherwise. He was being kept on small amounts of digitalis.

*Case 9.* P. R., male, aged 44. In April 1934 the patient experienced a very severe chest pain lasting for 24 hours. The cause was not recognized by the attending physician, and the patient was advised to use wet applications. In spite of the fact that he had fever he still tried to work but felt very weak and dizzy, and two weeks after the onset of the disease finally entered the hospital, where he remained six weeks. Since then anginal pain has made its appearance on rapid walking but never while at rest or when walking slowly. Ten months after the onset of the condition the patient came under our observation.

**Clinical findings:** A forceful pulsation was noted at the level of the fourth and fifth ribs, extending 2 cm. beyond the left midclavicular line and medially to the left parasternal line. The total width of the pulsation measured 9.5 cm. It extended upward to the third, and downward to the fifth interspace. The heart sounds were of low intensity. Murmurs were not heard. The heart rate was 72 per minute, and the rhythm was regular. Blood pressure was 135/65. **Electrocardiographic findings:** A deep Q-wave was present in Lead I, the initial downward deflection was absent in the chest lead. The R-T segment was isoelectric in the limb leads, while the S-T segment was depressed in the chest lead. T in Leads I and II was negative, in Lead III and in the chest lead positive.

Considering the history, the electrocardiographic findings, and the absence of hypertension in the past, the forceful precordial pulsation was interpreted as evidence of aneurysm of the anterior wall of the left ventricle.

**Radiologic examination:** The cardiac silhouette was considerably enlarged with an oblique diameter of 17 cm. The diaphragm was high in position. No abnormal bulge was noted. The area of the palpable cardiac thrust was mapped out by lead marks, and subsequent fluoroscopy revealed that the amplitude of pulsations over this area was very small, while the adjacent portions of the left ventricular border, particularly its basal portions, revealed a normal systolic inward movement.

A follow-up study three and a half years after the first attack of pain showed the patient satisfied with the condition of his health. He was capable of working as a tailor and also could do garden work. On walking rapidly, however, retrosternal pressure made its appearance.

Occasionally one has the opportunity to observe the development of both the palpable precordial pulsation and the bulge of the cardiac silhouette within a short time interval following the onset of anginal pain. This gives valuable aid in diagnosis.

*Case 10.* M. F., male, aged 56. This patient had been feeling well and did mountain climbing until the summer of 1935. A few months later he complained of an occasional jerking in the cardiac region, and often felt a drawing pain in the



location results merely in an elongation of the apical portion of the silhouette, such a finding being not characteristic in any way. Pathognomonic findings in the roentgenogram, however, may be expected for those cases where the aneurysmal formation involves the basal or middle portions of the left ventricle. One may then expect to find along a part of the left lower cardiac contour one or the other of the following findings: a localized bulge, a sudden kink, a centrifugal, systolic pulsation, calcification, shell-like in arrangement. The esophagus may reveal in its lower third either an impression from in front or a shallow deviation dorsad.

Electrocardiographic alterations indicating cardiac infarction were well marked in all of our cases and remained unchanged over a course of years. A deep S deflection in Leads II and III was strikingly noted in one half of the cases.

The prognostic outlook in the presence of cardiac aneurysm is relatively favorable. This refers both to expectation of life and to effort capacity.\*

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\* After completion of this article a paper of J. Parkinson, D. E. Bedford, and W. A. R. Thomson appeared (Quart. Jr. Med., 1938, vii, 455) dealing with cardiac aneurysm. The authors particularly stressed the importance of the radiological examination for the diagnosis of cardiac aneurysm and gave an excellent description of its radiological features. It seems to us that a thorough consideration of physical signs apart from roentgen-ray examination might considerably increase the number of diagnosed cases of cardiac aneurysm. Also a paper by Louis H. Zerk, Am. Heart Jr., 1939, xvii, 569-580, called attention to the cardiac aneurysm.

noted to show impression from in front and to deviate slightly dorsad. The rest of the clinical examination was negative. Examination of the urine showed nothing abnormal. Wassermann reaction was negative.

Reëxamination one year and nine months later showed the left nipple corresponding to the area of precordial pulsation quite prominent and approximately 1 cm. higher than the right nipple. The good effort capacity of the patient nearly two years following the cardiac infarction was quite remarkable. The patient was able to walk for one hour and a half at a good speed without stopping, and also could climb two flights of stairs without discomfort.

### DISCUSSION

Our observations together with the experience of other writers, indicate that cardiac aneurysm can be diagnosed in many cases during life. To be sure, many of the symptoms and signs to which the earlier writers refer, have proved to be of no value for diagnosis. Thus, for example, the often cited systolic and diastolic murmurs were not noted in any of our cases, although particular attention was paid to this point; nor have we ever heard a gallop rhythm. The attempt to percuss out a cardiac aneurysm, as has been tried by earlier investigators, need not be considered seriously. In some cases we have found a sign not described heretofore. Corresponding to the location of the aneurysm, there was noted a bulge of the precordial region, associated with a slight upward displacement of the left nipple. In not a few cases there was present a steady sensation of precordial pain; sometimes it could be elicited by pressure applied to a limited area of the chest, the area coinciding on the whole with the summit of the pulsating region of the wall of the chest. Yet this symptom, which Lutembacher<sup>2</sup> considered to be of diagnostic importance, was too ambiguous to be a dependable basis for the recognition of cardiac aneurysm.

Of all the diagnostic findings mentioned in the older literature of the subject, pulsations in the cardiac area have proved to be of greatest value. In nine of the ten cases which have been the subject of this inquiry, we were able to make the diagnosis of cardiac aneurysm primarily on the basis of a pulsatory finding. In only one case was the radiological examination of decisive value for the diagnosis. The precordial pulsation is the most frequent sign of cardiac aneurysm. The force and extent of this pulsation must naturally vary from patient to patient, depending upon the size of the aneurysm, the amount of thrombotic material lining the aneurysmal wall, the extent to which lung tissue intervenes between the cardiac and thoracic walls, and, finally, upon the thickness of the tissues overlying the bony chest wall. It will, therefore, be readily understood that pulsations of the chest wall are absent not only in cases of aneurysms affecting the posterior wall of the heart, but that in certain circumstances they may be missed even in those cases in which the aneurysmal bulge is located on the anterior wall of the heart.

The localization of the pulsation naturally depends upon the location of the aneurysm and upon the position of the diaphragm. In the great ma-

# STUDIES IN THE METABOLISM OF DEXTROSE FRAGMENTS IN MAN\*

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## INTRODUCTION

THE problem of producing a substitute carbohydrate for dextrose in the treatment of diabetes has been studied extensively by various investigators. This subject was comprehensively reviewed by Gottschalk<sup>1</sup> in 1929. Not any of the compounds studied has proved satisfactory from the point of view of being metabolized with a smaller amount of insulin than is dextrose. Moreover these compounds have defects as to availability, toxicity and taste. Perhaps the most promising substance studied for this purpose was dihydroxyacetone, investigated by Rabinowitch.<sup>2</sup> The possible merits of this substance at present, at least, are off-set by the cost of manufacture and its comparative instability.

In 1907, Nef<sup>3</sup> showed that when dextrose was treated with diluted, strongly dissociated alkalis the molecule theoretically could form 116 different substances of which he was able to identify 93; 47 of these were sugars and the rest fragments of sugar cleavage. Later Fischler<sup>4</sup> showed that dextrose treated with dilute alkali produced quantities of methyl glyoxal.

It occurred to the authors to study the metabolism of this mixture of sugar fragments as an entity. Its possible use as a substitute carbohydrate in diabetes suggested itself.

## PREPARATION OF ALKALINIZED DEXTROSE

Alkalinized dextrose was prepared according to the method of Nef.<sup>5</sup> A cold solution of 100 grams of dextrose in 500 c.c. of water was shaken with 0.5 gram of calcium oxide and heated at 70° for an hour; then an additional 0.5 gram of calcium oxide was added and the temperature was maintained at 70° for another hour. This last operation was repeated. The dark red, neutral solution obtained was distilled under diminished pressure to remove water until 100 c.c. of the syrupy solution remained. One cubic centimeter of this solution represents one gram of dextrose employed. The fate of dextrose submitted to this calcium hydroxide treatment was followed polariscopically. The reduction in optical activity was prompt and uniform in

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The authors wish to acknowledge their indebtedness to the Department of Medicine of this School for their coöperation in supplying diabetic subjects for this test.

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of the left ventricle is best visible with the patient in the right oblique anterior position. Calcium deposits in the wall of the aneurysm were observed only once in our series.

Wolferth, Wood and Bellet<sup>18</sup> reported a case of a large aneurysm of the posterior wall in which the difficult passage of barium through the lower third of the esophagus attracted attention. In five of the seven cases which we examined especially with this in mind, we were able to observe in the right anterior oblique view at the lower third of the esophagus a slight impression from in front and a dorsal displacement at this level. These cases had shown no signs of cardiac failure. We were not able to decide whether these changes in the esophagus were caused by a dilation of the left atrium, as a result of inclusion in the process of infarction; or whether they were due to a backward displacement of the left ventricle, whose anterior portion was the seat of the aneurysm, as has been suggested by other observers.<sup>8, 22</sup>

The radiological examination revealed in seven cases definite enlargement to the right, and this in patients who had never shown signs of cardiac insufficiency. Similar changes were noted in two cases of cardiac aneurysm in another series of topographical anatomical studies, on which we shall report in detail later. In those cases a very considerable distention of the anterior wall of the left ventricle, chiefly towards the right, was observed, which resulted in a shifting of the anterior longitudinal sulcus towards the sternum. Associated with this was a displacement of the right ventricle; its right contour, which normally coincides with the right margin of the sternum, was displaced far laterad.

In one half of our cases the radiological study revealed no characteristic changes. Yet the percentage of cardiac aneurysm without pathognomonic radiological changes is obviously higher, for in this study we have included only those cases where there was no doubt as to the diagnosis, and a considerable number of cases escape clinical diagnosis and are discovered only at autopsy. In such cases the radiological examination reveals only an enlargement of the apical region which has no special characteristics.<sup>19</sup> Often a small pulsatory amplitude along the left ventricular margin has been noted. Many authors<sup>2, 12, 19</sup> have remarked on the rarity of characteristic radiologic findings. In order to understand this fact it should be remembered that not all cases of cardiac aneurysm reveal a bulge along the surface of the heart. Often they merely form shallow pittings on the inner surface of the ventricle, which are only perceptible upon inspection of the interior of the heart.<sup>20</sup> The resistance of the fibrous, attenuated ventricular wall may be considerably strengthened by thickening of the epicardium, by an adherent pericardium, and further, by the deposit of layers of thrombotic clot along the inner surface, so that both circumscribed bulge and abnormal pulsatory phenomena may be absent.<sup>15</sup> Moreover, among the cases of cardiac aneurysm with a bulge of the ventricular wall are only those accessible to radiological diagnosis, where the aneurysm is not confined to the apical

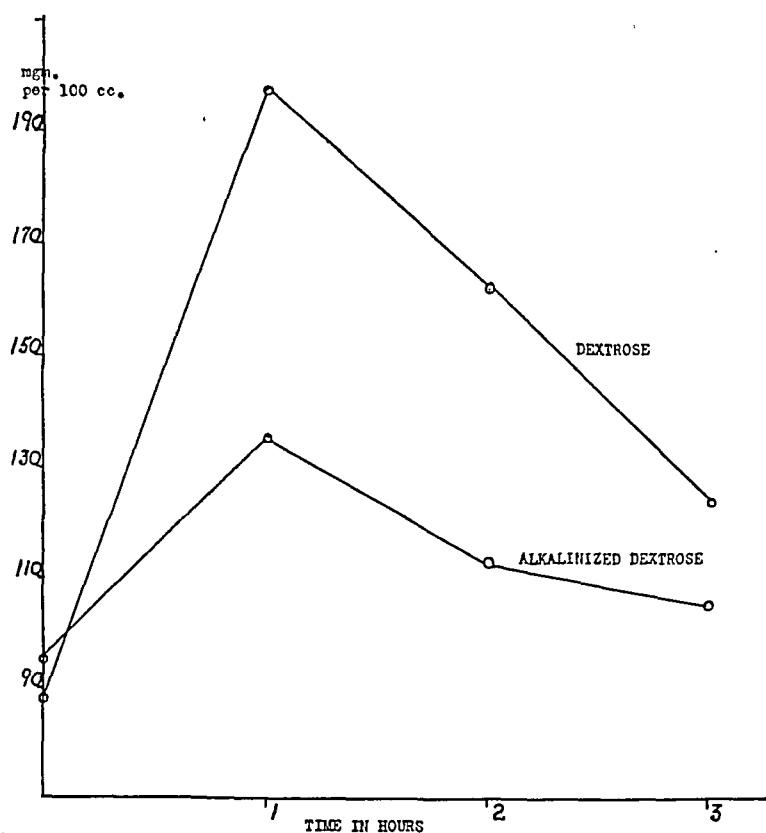


CHART I. Action of dextrose and alkalinized dextrose on the blood-sugar of rabbits orally.

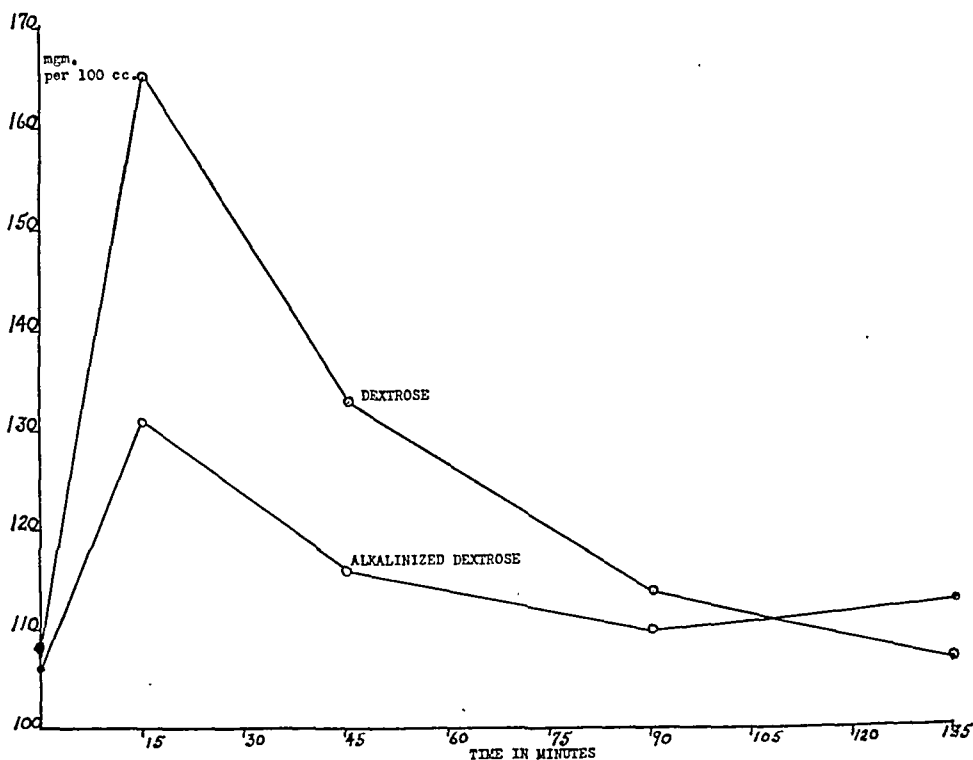


CHART II. Action of dextrose and alkalinized dextrose on the blood-sugar of rabbits intravenously.

death occurred in two; in one three months and in the other four years after the onset of the coronary artery occlusion. Eight patients are still living, and in these the periods of survival following the occlusion are as follows: one, two, three, three and a half, four, four, six and seven years, respectively.

The capacity of these patients for physical effort is quite striking. When we learn that a patient with a large cardiac aneurysm is able to ascend the stairs to his fourth-story apartment at a normal speed without distress; that another has been the subject of a gastrectomy without any ensuing cardiac complications; and, finally, that still another is able, despite his cardiac aneurysm, to ski, to walk for 10 hours on end and to climb a mountain with an altitude of 6,000 feet, these facts give us a vivid impression of the astounding physical capacity of such hearts. Our observations agree with the experience of other authors,<sup>5, 15, 17</sup> who report upon satisfactory cardiac function in patients suffering from cardiac aneurysm. If the muscular structure of the heart as a whole is not seriously injured, it would appear that quite a considerable part may be out of function and that this condition is borne relatively well. Experience with cases in which rather extensive destruction of the heart muscle by malignant tumors has occurred is in agreement with this opinion.<sup>21</sup>

#### SUMMARY

Ten cases are reported in which the diagnosis of cardiac aneurysm was made during life. In two of these cases the diagnosis was verified by postmortem examination, while in five cases characteristic radiologic findings were obtained.

The diagnosis of cardiac aneurysm is based primarily on physical examination. On palpation one finds a large and forceful cardiac thrust, which, depending upon the site of the aneurysm, is located either within the midclavicular line or outside of it, and most commonly at the level of the fifth rib. The diffuse character of the thrust, its considerable width, and particularly its medial extension, are significant features in diagnosis. The area of pulsation is likely to be situated more cranial than one would expect for the apical thrust caused by an hypertrophied left ventricle. Such a pulsation is of significance for the diagnosis of cardiac aneurysm, if the history and the electrocardiographic findings indicate a preceding cardiac infarction, and if other causes for such a forceful cardiac thrust, such as hypertension or mitral and aortic valvular lesions, can be excluded. It is especially significant if the development of such a pulsation can be observed subsequent to a coronary artery occlusion.

In our material we have not observed murmurs nor any particular findings obtained by means of percussion.

The radiological examination revealed characteristic features only in half of our cases. This should be explained by the fact that the aneurysmal development is most often limited to the apical portion of the heart. This

five grams were given after fasting and 25 grams one half hour later. The average of these results is shown in chart 3.

A study of table 1 and of this average value indicates that the low blood-sugar curves observed when alkalinized dextrose was administered to rabbits did not obtain in normal man.

A series of 12 moderately severe diabetics were studied according to the divided-dose tolerance tests. These results are shown in chart 3.

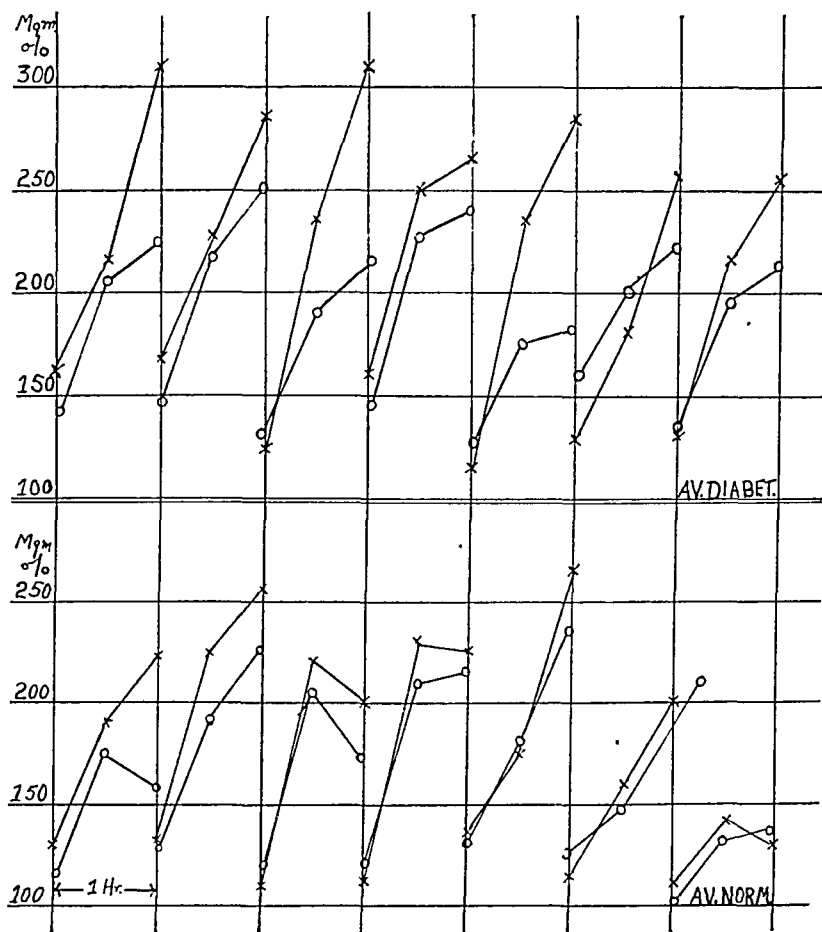


CHART III. Action of dextrose and alkalinized dextrose on the blood-sugar of diabetic subjects.

x Dextrose.  
o Alkalinized Dextrose.

### DISCUSSION OF RESULTS

The treatment of dextrose with strongly dissociated alkali solutions according to Nef<sup>3</sup> causes the hexose to undergo degradation into simpler molecules. The first effect of the hydroxyl ion is a likely rearrangement of the dextrose molecule into its  $\beta$  and  $\gamma$  forms. The more labile forms then produce alkali glucosate with the rupture of the oxide ring and finally undergo cleavage into three carbon-atom chains. Among the more common

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and alkalinized dextrose in 12 moderately severe diabetics, the hyperglycemia with the latter in all instances was less than that produced when dextrose was ingested (chart 3). In diabetes, where possibly the utilization of dextrose is disturbed to a greater degree than the polymerization of this sugar, this substance seems to warrant further trial. On the basis that polymerization is necessary to the catabolism of alkalinized dextrose, the possibility of diminishing post-prandial hyperglycemia presents itself. Besides, the desirable taste and the inexpensiveness are factors of practical importance. The authors commend the further study of this substance as a substitute carbohydrate in diabetes in institutions where a large diabetic service is available.

### SUMMARY

The metabolism of alkalinized dextrose in animals, normal and diabetic man has been studied and compared with that of dextrose. Its possibility of use as a substitute carbohydrate in diabetes has been discussed.

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consecutive samples treated by the foregoing procedure. The dextrose reached a minimal specific rotatory power of  $[\alpha]_{\frac{25^\circ}{D}} + 3.7$  after the complete treatment, as evinced by the fact that subjecting the same mixture to the process again did not effect any change in optical activity. Six months standing under laboratory conditions did not alter the rotation. Varying quantities of dextrose were added to a 5 per cent solution of alkalinized dextrose and the rotation was determined immediately. The addition of 5 per cent dextrose to alkalinized dextrose changed the rotation of  $[\alpha]_{\frac{25^\circ}{D}} + 3.7$  to  $[\alpha]_{\frac{25^\circ}{D}} + 7.7$ ; the addition of 1 per cent gave a value of  $[\alpha]_{\frac{25^\circ}{D}} + 5.0$ . Smaller quantities of unaltered dextrose could not be detected by this method.

The copper reducing power (Fehling's solution, Munson-Walker method) is quantitatively the same as dextrose. However, at  $25^\circ$  the quantities of cuprous oxide formed by alkalinized dextrose measured at 15 minute intervals over one hour were approximately three times greater than those produced by dextrose under the same conditions.

The heat of combustion per c.c. is 3.17 calories compared with 3.74 calories per gram for unaltered anhydrous dextrose.

Optical rotation studies, reduction tests and the constancy of caloric value in consecutive samples indicate that alkalinized dextrose is uniform in composition and the authors believe that there is no dextrose in the mixture that has not been altered by the alkali treatment.

#### METHOD OF STUDY

Elsewhere<sup>6</sup> the authors have shown that in rats, dogs and rabbits dextrose treated in this manner is not toxic. Furthermore, the substance was shown to be capable of being utilized by the rat as evidenced by additional glycogen storage in the liver. However, the feeding of alkalinized dextrose by stomach tube did not significantly raise the respiratory quotient of the rat during  $2\frac{1}{2}$  hour periods, when measured by a modification of Haldane's open circuit apparatus.<sup>7</sup> In the rabbit alkalinized dextrose produced only a very mild hyperglycemia when administered by stomach tube (nine experiments) or by vein (22 experiments); a summary of these results is shown in charts 1 and 2.

These findings prompted experiments on normal and diabetic humans. Eight-tenths of a gram of dextrose and 0.8 c.c. of alkalinized dextrose respectively, per pound of body weight, were administered orally to previously fasted normal individuals allowing at least 48 hours to elapse between tests. The blood sugars were determined by the Folin<sup>8</sup> micro method. The results are set forth in table 1.

Another series of 12 normal individuals were given dextrose and alkalinized dextrose tolerance tests using the divided dose method. Twenty-

sion; (2) the rectal temperature at the end of 36 hours of treatment; (3) the concentration of free sulfapyridine in the blood; (4) change in the number of leukocytes. Vomiting occurred at some time during treatment in about 80 per cent of the patients. Bacteremia and extensive consolidation of the lungs were considered indications for giving the maximum amount of the drug which the patient could tolerate.

The largest dose (98 gm. in 11 days) was given in Case 5 (figure 1), a patient admitted on the seventh day of the disease with symptoms of virulent infection. On admission, 200,000 units of anti-pneumococcus rabbit serum were given because the supply of sulfapyridine was temporarily exhausted. The serum appeared ineffective and 24 hours later sulfapyridine was begun. Nine grams were given daily for five days. Although the bacteremia disappeared promptly, clinical improvement was slow. Seven grams were therefore given daily during the next six days. Neither leukopenia nor anemia occurred.

## RESULTS

An unselected group of 50 patients was treated with sulfapyridine during the fall and winter of 1938-1939. Recovery was surprisingly rapid when treatment was begun early. The fall of temperature and leukocytes

TABLE I  
State of Patients Treated with Sulfapyridine

Type	No. of Cases	No. Cases over 40 yrs. Age	Duration more than 3 days	No. Lobes Consolidated			Bacteremia	Empyema or Effusion	Extension	Avg. Maximum Blood Conc. mg. 100 c.c.	Died
				1	2	3					
I	9	3	3	2	5	2	3	1 Empyema	0	8 mg.	0
III	6	5	0	4	2	0	0	1 Empyema 1 Effusion	1	6 mg.	0
IV	4	3	0	1	3	0	0	0	1	4 mg.	0
V	14	1	8	4	8	2	4	2 Effusion	1	6.5 mg.	1
VI	1	0	1	1	0	0	0	0	0	7.3 mg.	0
VII	6	2	5	2	4	0	0	1 Empyema	2	4.5 mg.	0
VIII	2	1	0	0	2	0	0	0	0	4.1 mg.	0
XII	1	0	0	1	0	0	0	0	0	3 mg.	0
XIV	3	2	3	1	1	1	1	0	1	16 mg.	2
XVIII	1	0	1	0	1	0	0	0	0	5.8 mg.	0
XIX	1	0	0	0	1	0	0	0	0	8 mg.	0
XXIII	1	0	1	0	1	0	0	0	0	6 mg.	0
XXIX	1	0	1	0	1	0	0	0	0	7 mg.	0
Total	50	17	23	16	29	5	8	3 Empyema 3 Effusion	6		3

was impressive (figure 1) with the pulse and respiration rate shortly following. The symptoms and signs of infection quickly left the patient and were replaced by a feeling of well being. This change of state was striking and might occur within 24 hours. One often saw a patient who on admis-

TABLE I  
Blood Sugar Curves in Man

Subject No.	Weight lbs.	Substance Administered	Mg. per 100 c.c. blood						Urinary sugar End of 1 hour
			Fasting	$\frac{1}{2}$ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.	
1	216	Dextrose	59	164	183	182	194	166	+
		Alkalinized dextrose	103	162	190	151	141	139	++
2	104	Dextrose	91	183	179	165	159	129	++
		Alkalinized dextrose	100	151	192	132	129	119	+++
3	128	Dextrose	100	139	143	114	103	93	-
		Alkalinized dextrose	93	131	113	121	96	102	+
4	132	Dextrose	105	88	156	180	99	lost	lost
		Alkalinized dextrose	100	154	133	125	122	lost	-
5	126	Dextrose	87	185	163	111	87	lost	+
		Alkalinized dextrose	100	188	210	145	83	86	++++
6	167	Dextrose	101	97	96	98	96	98	-
		Alkalinized dextrose	93	110	92	91	87	90	+
7	145	Dextrose	108	123	156	143	120	lost	-
		Alkalinized dextrose	87	130	118	120	117	lost	-
8	113	Dextrose	96	196	194	134	133	117	+
		Alkalinized dextrose	99	183	156	105	108	94	+
9	152	Dextrose	100	183	169	126	96	90	+
		Alkalinized dextrose	98	143	165	130	122	100	++
10	165	Dextrose	85	166	121	116	98	77	-
		Alkalinized dextrose	97	143	115	128	104	96	++
11	162	Dextrose	91	140	143	112	98	88	-
		Alkalinized dextrose	94	170	112	100	108	95	+++
12	151	Dextrose	97	106	133	119	104	90	-
		Alkalinized dextrose	119	157	149	144	122	118	++++
13	130	Dextrose	96	123	131	102	94	100	-
		Alkalinized dextrose	99	171	160	165	134	96	++++
14	136	Dextrose	91	129	136	107	94	89	-
		Alkalinized dextrose	98	135	148	140	108	99	++++
15	150	Dextrose	93	155	170	124	118	96	-
		Alkalinized dextrose	105	164	120	170	112	105	++++
16	140	Dextrose	82	200	155	119	74	81	-
		Alkalinized dextrose	91	169	154	161	109	92	++++
17	167	Dextrose	105	178	133	122	110	95	-
		Alkalinized dextrose	105	152	118	146	129	126	++
18	155	Dextrose	93	119	164	115	89	86	+
		Alkalinized dextrose	94	156	137	154	121	95	++++
Average	.	Dextrose	93	150	151	127	109	99	
		Alkalinized dextrose	98	154	143	135	114	92	

sion was restless, sweating, apprehensive, and tachypneic, obviously desperately ill, change within 24 hours to one who appeared well. Crisis occurred in 41 patients within 36 hours after treatment was initiated. The fall in six patients was by lysis. It is important that the fever was not affected by the drug in two of the patients who died.

We have been unable to establish a direct relationship between dosage and concentration of free sulfapyridine in the blood. Large doses several times failed to raise the blood level to the high concentrations observed in other patients who received smaller amounts of the drug.

Eight patients recovered when the maximum blood concentration of free sulfapyridine averaged less than 3 mg. per 100 c.c. A high concentration does not insure recovery as demonstrated by the fact that in our fatal cases the maximum concentrations were respectively 18 mg., 14 mg., and 11 mg. per 100 c.c.

### DEATHS

Death occurred in two patients with Type XIV infection. One of these, Case 45 (figure 7), was admitted on the fifth day of the disease with three lobes of the lung involved. Pulse and respiratory rate were disproportionately rapid. Repeated blood cultures showed no bacteremia. Forty-four grams of sulfapyridine were given within four days without effect on temperature or leukocytes. The concentration of sulfapyridine in the blood reached a maximum of 18 mg. per 100 c.c., yet no evidence of toxicity was observed. Although there was an abundance of free sulfapyridine in the blood, it proved ineffective. Type specific anti-pneumococcus serum might well have been given.

The second patient who died, Case 50 (figure 8) with a Type XIV infection was admitted on the fourth day of the disease with consolidation of the lower lobe of the right lung. Bacteremia was demonstrated by two blood cultures. Sulfapyridine produced a fall in temperature and disappearance of the bacteremia in 36 hours. It was given for four days and then discontinued because vomiting was severe. Twenty-four hours later the pneumonic process extended into the upper lobe of the right lung and bacteremia recurred. Simultaneous sulfapyridine and specific anti-pneumococcus serum therapy (100,000 units) was instituted with resulting disappearance of fever. A four day period of clinical improvement was followed by another recurrence of chills and fever. Since pyuria and bacteriuria were found, it suggested that the cause of this relapse was pyelitis. Sulfanilamide was employed instead of sulfapyridine but the temperature continued to be elevated. Cardiac murmurs indicative of aortic insufficiency along with the peripheral vascular signs which accompany such defects, were observed on the fifth day of the recurrence. Type XIV pneumococcic bacteremia was again observed. The patient died eight days after the onset of this relapse and 26 days after admission to the hospital. Post-mortem examination revealed acute bacterial endocarditis with extensive

products identified by Nef were methyl glyoxal, glyceric aldehyde, glyceric acid, trihydroxybutyric acid, tetrahydroxyvaleric acid and glycollic acid. The lowered oxygen consumption upon combustion indicates that partial oxidation has occurred. It was the thought of the authors that these sugar fragments might catabolize in the body directly (without conversion into glycogen) with a lesser amount of insulin or perhaps elicit the secretion of more insulin from the impaired islet tissue as Gottschalk<sup>1</sup> suggests is true of fructose and dihydroxyacetone.

Results of glycogen storage in the liver of the white rat showed definitely that there is no significant difference between glycogen storage as induced by the feeding of dextrose and that caused by the feeding of alkalinized dextrose. This indicates the capacity of alkalinized dextrose to form glycogen.

The inability of alkalinized dextrose to increase the respiratory quotient or the oxygen consumption of the rat indicates that the direct utilization of the mixture in the animal body is unlikely, and that its metabolism will occur only after previous conversion into glycogen. Kermack<sup>9</sup> et al. have shown that dihydroxyacetone may be directly utilized by the body tissues, yet Ringer<sup>10</sup> and Frankel have demonstrated that this triose is almost quantitatively converted into dextrose in the animal body.

Like dihydroxyacetone, alkalinized dextrose combats insulin shock in mice.

The curves for the blood-sugar levels of rabbits with dextrose and alkalinized dextrose are strikingly dissimilar. By oral and intravenous administration, the hyperglycemia produced by alkalinized dextrose was far less marked than that produced by dextrose. We attribute this to the rapid polymerization of the sugar fragments into glycogen thus causing a diminution of reducing substances in the blood.

In normal man, table 1 and chart 3 show that this condition does not obtain and that the hyperglycemia determined as dextrose produced by each substance is substantially the same. We are unable to offer any explanation for this difference in response to alkalinized dextrose between the rabbit and man unless the liver of the rabbit is better capable of polymerizing the fragments of the dextrose molecule than the liver of man. In this connection it is interesting to note that Grevenstuk and Laquer<sup>11</sup> observed that dihydroxyacetone given intraperitoneally to mice and rats was converted into glycogen, but when given orally to man the substance produced lactic acid which appeared in the blood and urine.

It is interesting to note that most of the individuals showed a transient glycosuria with alkalinized dextrose which, however, was not sufficient to account for the difference in blood sugar in diabetics, assuming the absorption to be the same as that of untreated dextrose. Perhaps some strongly reducing dextrose fragments in the urine were responsible for this observation.

In normal man the degrees of hyperglycemia with dextrose and alkalinized dextrose were practically the same. With smaller quantities of dextrose

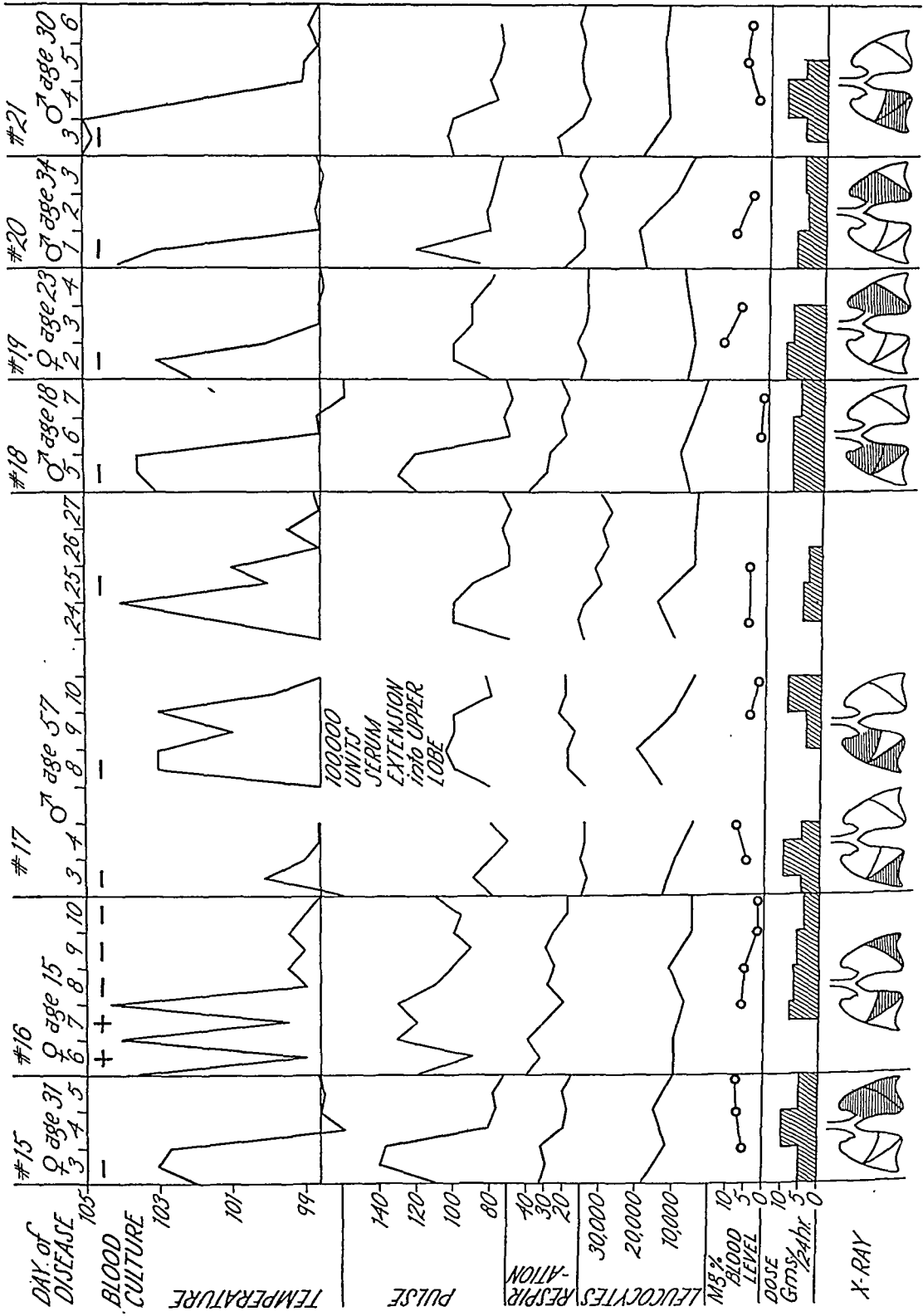


FIG. 3. Clinical summary of seven patients with Type V infection.

# THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA WITH SULFAPYRIDINE\*

By K. G. KOHLSTAEDT, M.D., and IRVINE H. PAGE, M.D.,  
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SEVERAL communications dealing with the clinical applications of sulfapyridine (2 sulfanyl-amino-pyridine) have appeared since Whitby's (1938) report of its value in the control of pneumococcic infections in mice. Among the first of these and one of great importance, is that of Evans and Gaisford (1938), which gave hope that a drug of value had been discovered. Subsequent work is confirming this belief.

The purpose of this communication is to describe our experience in the treatment of pneumococcic pneumonia in the Indianapolis City Hospital and in the private pavillion of the Methodist Hospital during the fall and winter of 1938-1939.

## METHODS

All patients with pneumococcic pneumonia were treated with sulfapyridine. The following procedures other than routine examinations were employed to verify the diagnosis and follow the course of the disease: sputum typing, blood cultures, blood counts, roentgenograms, occasional lung puncture and urea clearance tests. Determination of the amount of free sulfapyridine in the blood was made by a modification of the method of Schmidt (1938) in which the concentration of sodium  $\beta$ -naphthoquinone-4-sulfonate was increased from 0.2 per cent to 0.5 per cent. The color thus obtained follows Beer's law more closely than that given by the weaker reagent. The color intensity was measured with the Evelyn photoelectric colorimeter. We are indebted to Dr. O. M. Helmer of the Lilly Laboratory for Clinical Research, through whose courtesy these determinations were made.

Oxygen and other supportive measures were used wherever the clinical condition of the patient indicated the need. The patients were treated in the wards without special nursing care.

## DOSAGE

The total amount of sulfapyridine given varied markedly from patient to patient but the dose during the first 36 hours was standardized. Treatment was begun with an initial dose of 2 gm. followed by 1 gm. at two or three hour intervals during the next 36 hours. This approximated a total dose of 1 grain per pound or 0.12 gm. per kg. during this period.

Further administration of the drug depended on: (1) the severity of toxic manifestations, i.e., vomiting, skin rash, mental confusion or depres-

\* Received for publication July 13, 1939.



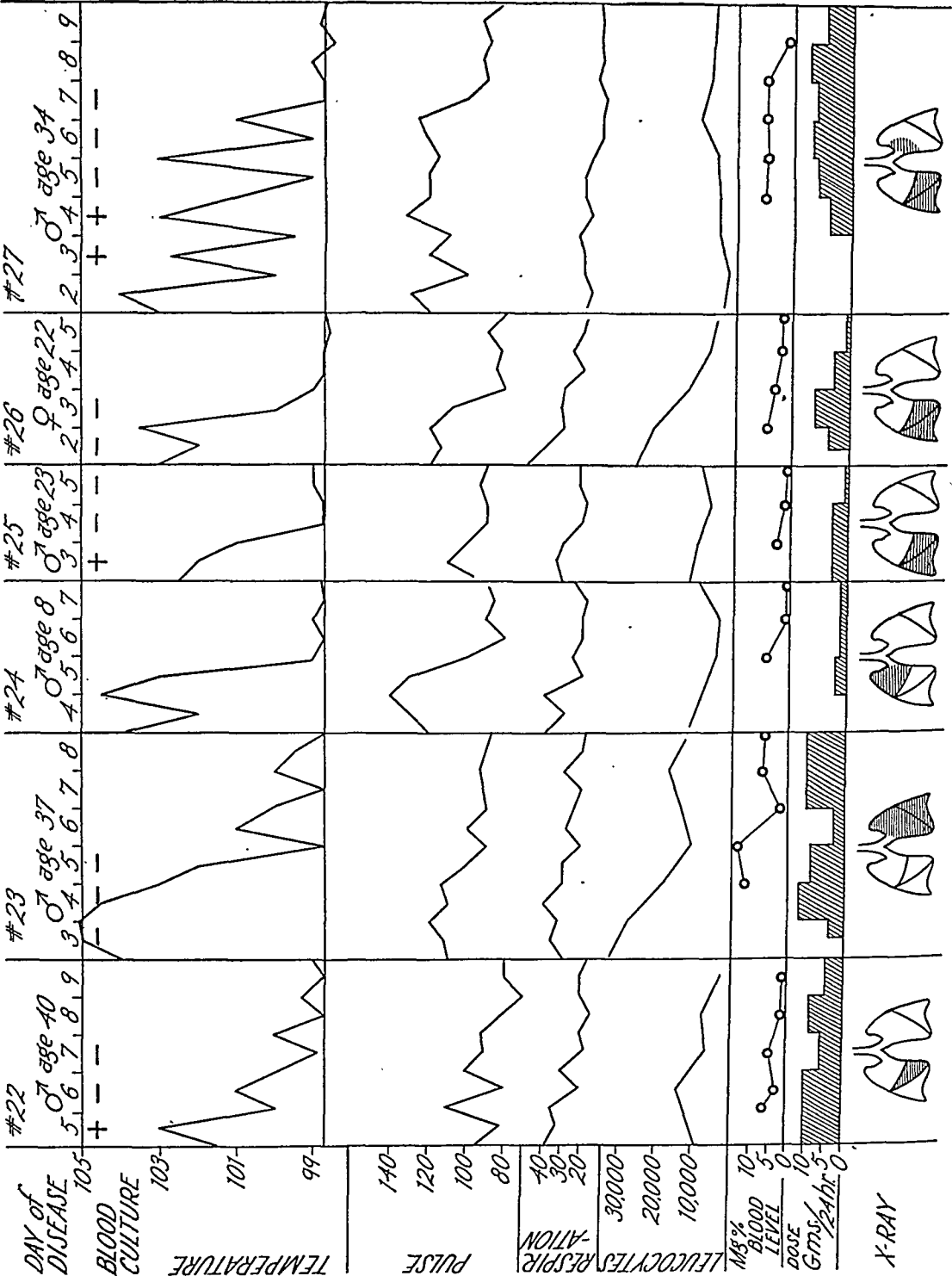


FIG. 4. Clinical summary of six patients with Type V infection.

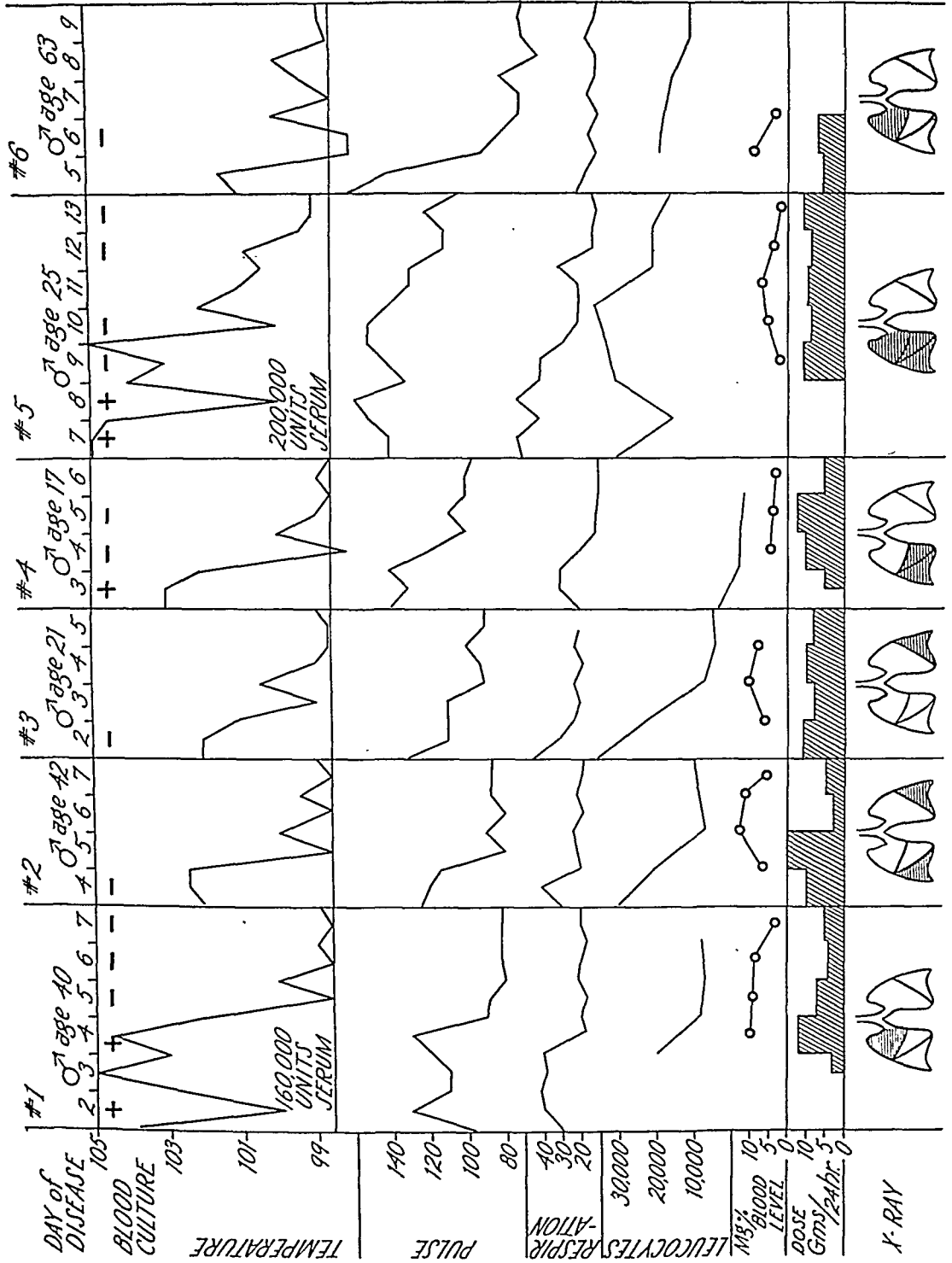


FIG. 1. Clinical summary of six patients with Type I infection.

A clear, sterile effusion occurred during the course of pneumonia in three other patients. The fluid did not reappear after a single aspiration.

### EXTENSION OF PNEUMONIA

When the fever disappears and the pulse rate returns to normal, the physician tends to feel that the patient is cured. But it is just at this time, in our experience, that he needs sharp observation to detect recrudescence.

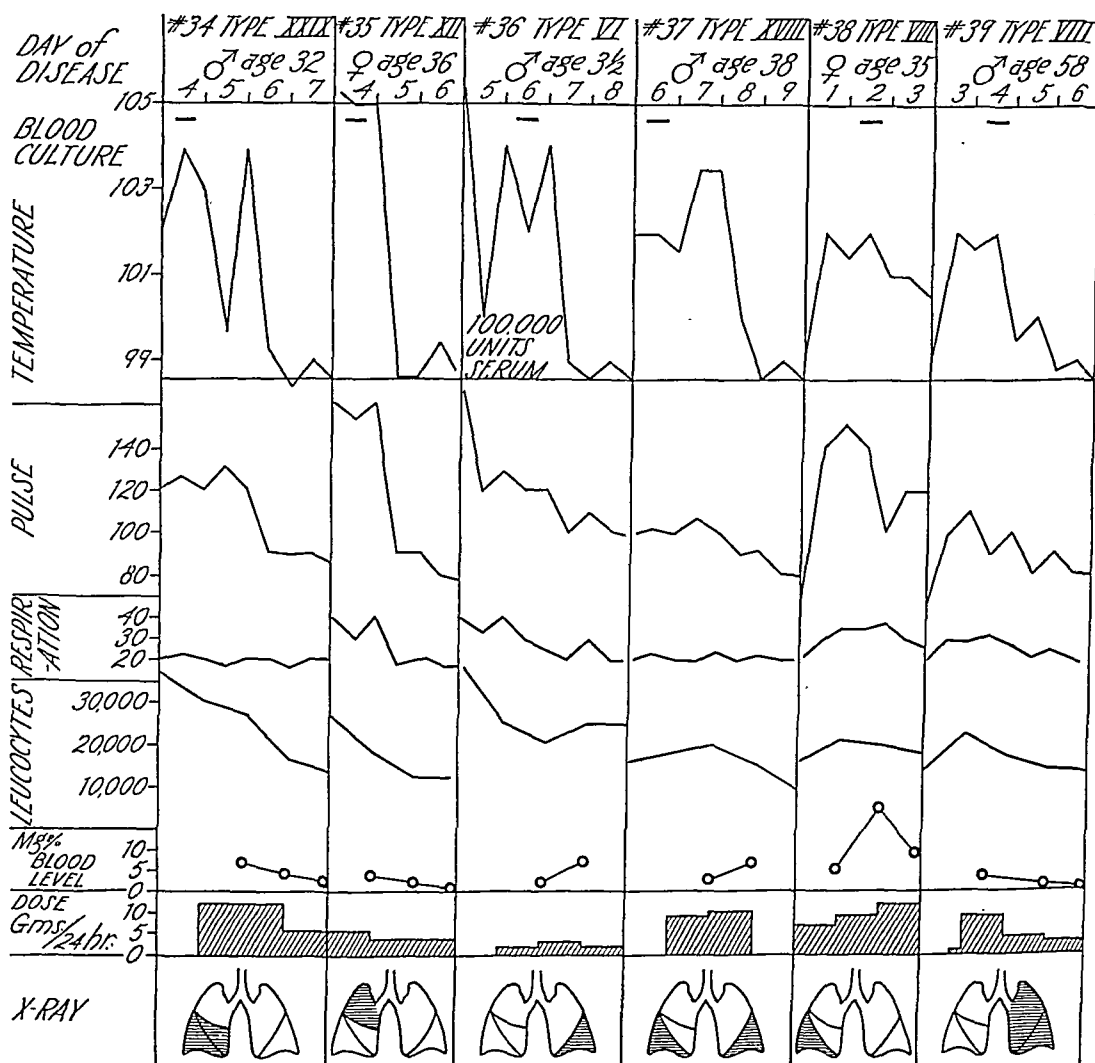


FIG. 6. Clinical summary of six patients with infection of Types XXIX, XII, VI, XVIII, and VIII.

In four patients extension of the pneumonic process occurred after the drug had been discontinued, but in these it had been discontinued not because the patient was considered well, but because of (a) leukopenia (3 patients) and (b) severe vomiting (one patient). Extension occurred in two patients in spite of what appeared to be adequate amounts of sulfapyridine in the blood.

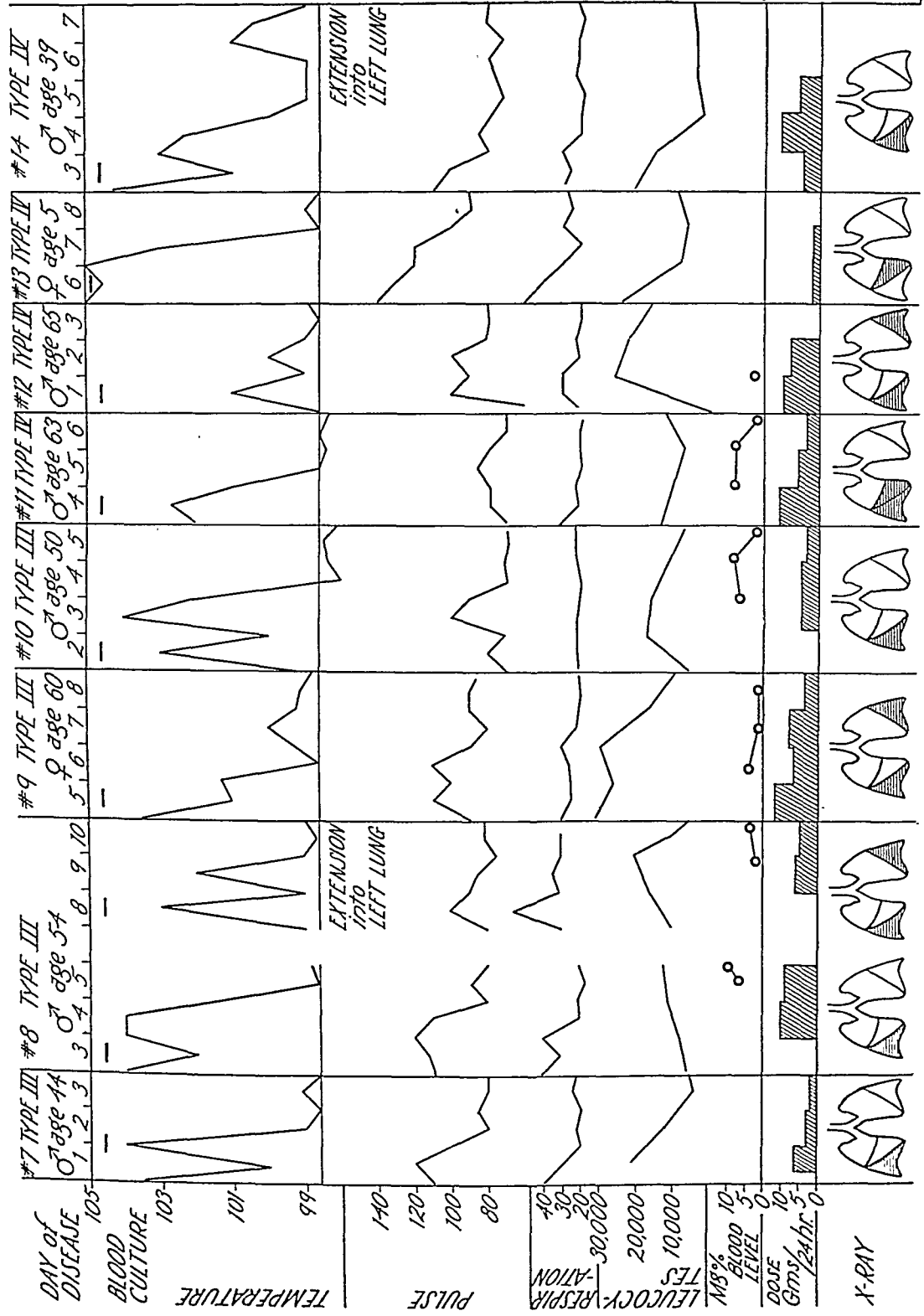


FIG. 2. Clinical summary of four patients with Type III infection and four with Type IV infection.

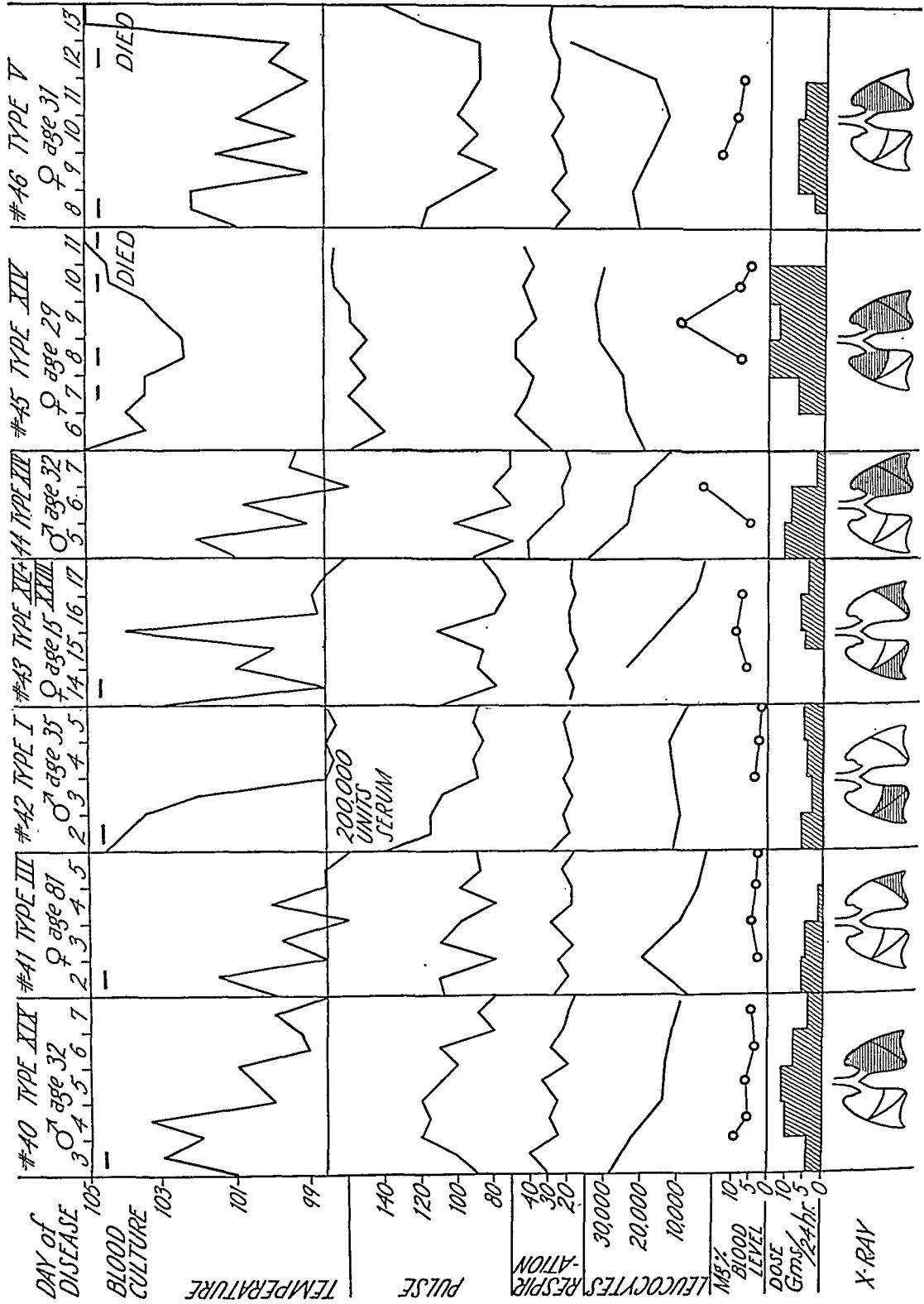


Fig. 7. Clinical summary of seven patients with infection Types XIX, III, I, XV and XXIII, XIV, and V.

necrosis of the cusps of the aortic valve and underlying myocardium. The renal parenchyma was studded with minute abscesses from which Type XIV pneumococci were cultured.

The infection in the third fatal case, Case 46 (figure 7), was caused by a Type V pneumococcus. She had vomited repeatedly since the onset of the disease seven days before admission. Blood cultures were negative. Twenty-three grams of the drug were given in the course of three days, which elevated its concentration in the blood to 14 mg. per 100 c.c. Vomiting continued; the abdomen was rigid and the patient appeared desperately ill. On the fourth day shock occurred suddenly and did not respond to treatment with intravenous sodium chloride, acacia and blood transfusion. Death occurred 24 hours after the onset of shock. Postmortem examination revealed consolidation of the upper lobe of the right lung and a resolving pneumonic process in the lower lobe. An acute ulcer whose histological characters suggested its recent formation was found in the cardiac portion of the stomach. A local fibrinous peritoneal exudate overlay the ulcer which, however, had not perforated into the peritoneal cavity.

#### BACTEREMIA

Seven of eight patients with bacteremia recovered. One patient died as a result of acute pneumococcic endocarditis involving the aortic valve. The bacteremia in four was due to a Type V organism, in three to a Type I, and in one to a Type XIV.

In two of the patients with Type I infections, specific anti-pneumococcus rabbit serum was given prior to sulfapyridine because the supply of the drug was temporarily exhausted. In a patient, Case 50 (figure 8), with Type XIV pneumonia, the initial bacteremia was treated with sulfapyridine and its recurrence with simultaneous sulfapyridine and serum. This combined treatment was used because the patient had not tolerated the sulfapyridine during the 24 hours preceding the onset of the recurrence and because extension of the pneumonia with recurrence of bacteremia had taken place when sulfapyridine alone had been used.

The remaining five patients received only sulfapyridine and in larger amounts (50 to 98 gm. total dose) than patients without bacteremia. This may account for the fact that leukopenia and anemia were observed in two of them.

The recurrence of bacteremia and development of acute bacterial endocarditis in one patient when administration of sulfapyridine was discontinued suggest the desirability of prolonged administration to patients with bacteremia. Within 24 hours after sulfapyridine is begun, the blood stream is often found free of bacteria.

Defervescence was by lysis in six patients in the bacteremic group and in two patients by crisis.

sulfapyridine in 15 days. The red blood cells decreased from 4,100,000 with 80 per cent hemoglobin to 2,400,000 with 49 per cent hemoglobin. The white blood cell count was 21,000 when treatment was begun and decreased to 16,000.

#### EFFECT OF SULFAPYRIDINE ON THE KIDNEYS

Examination of the urine of patients treated with sulfapyridine suggested that in most patients it had no harmful effects on the kidneys. However, in two patients marked hematuria occurred after large doses. The drug was discontinued and within three days the hematuria abated.

That the drug may be given without necessarily further injuring the kidneys of patients with renal insufficiency is illustrated by Case 47 (figure 8). The infection was caused by Type III pneumococcus, and urea clearance was found to be 10 per cent of normal. After 9 grams of sulfapyridine were given the blood level was 4 mg. per 100 c.c.; the drug was then discontinued because of vomiting. However, the concentration in the blood did not decrease nearly as rapidly as we had learned to expect in patients with normal kidneys. The patient was well on the fifth day after onset of the disease. Urea clearance on the fifteenth day was 14 per cent normal.

#### CYANOSIS

Moderate cyanosis was present in the majority of patients before treatment with sulfapyridine. It could be controlled by oxygen and usually disappeared after crisis occurred. At no time was cyanosis observed comparable to that commonly noted after large doses of sulfanilamide. We found no correlation between cyanosis and the onset of other signs or symptoms associated with the toxic action of the drug.

#### DISCUSSION

The mortality from pneumococcic \* pneumonia in patients receiving no specific treatment in this hospital for the past two years has been 48 per cent (197 patients) and 33 per cent (147 patients) respectively. There is no reason to suppose that it would have been less this year. We have seen few of the so-called "virus" pneumonias which appear to be common in the eastern states. In the 50 patients receiving sulfapyridine the mortality was only 6 per cent, yet 17 of the patients were over 40 years of age. The onset of the pneumonia was three or more days before treatment was begun in 23 patients; six were infected with Type III pneumococci and bacteremia occurred in eight patients. The patients were treated on open wards of a hospital for the indigent without special nursing care. This result, in our opinion, leaves little room to doubt the value of the treatment.

When treatment is begun early, clinical improvement is usually surprisingly rapid and clearing of the morbid changes in the lungs soon follows.

\* The bacteria were not typed in all of these patients.

## EMPYEMA

Two patients developed pneumococcic empyema during treatment with sulfapyridine. In both, Cases 48 and 49 (figure 8), the free sulfapyridine was repeatedly observed to be 6 mg. per 100 c.c. in the blood, yet a purulent effusion occurred and organisms which could be typed were cultured from the chest fluid. Surgical intervention ultimately became necessary.

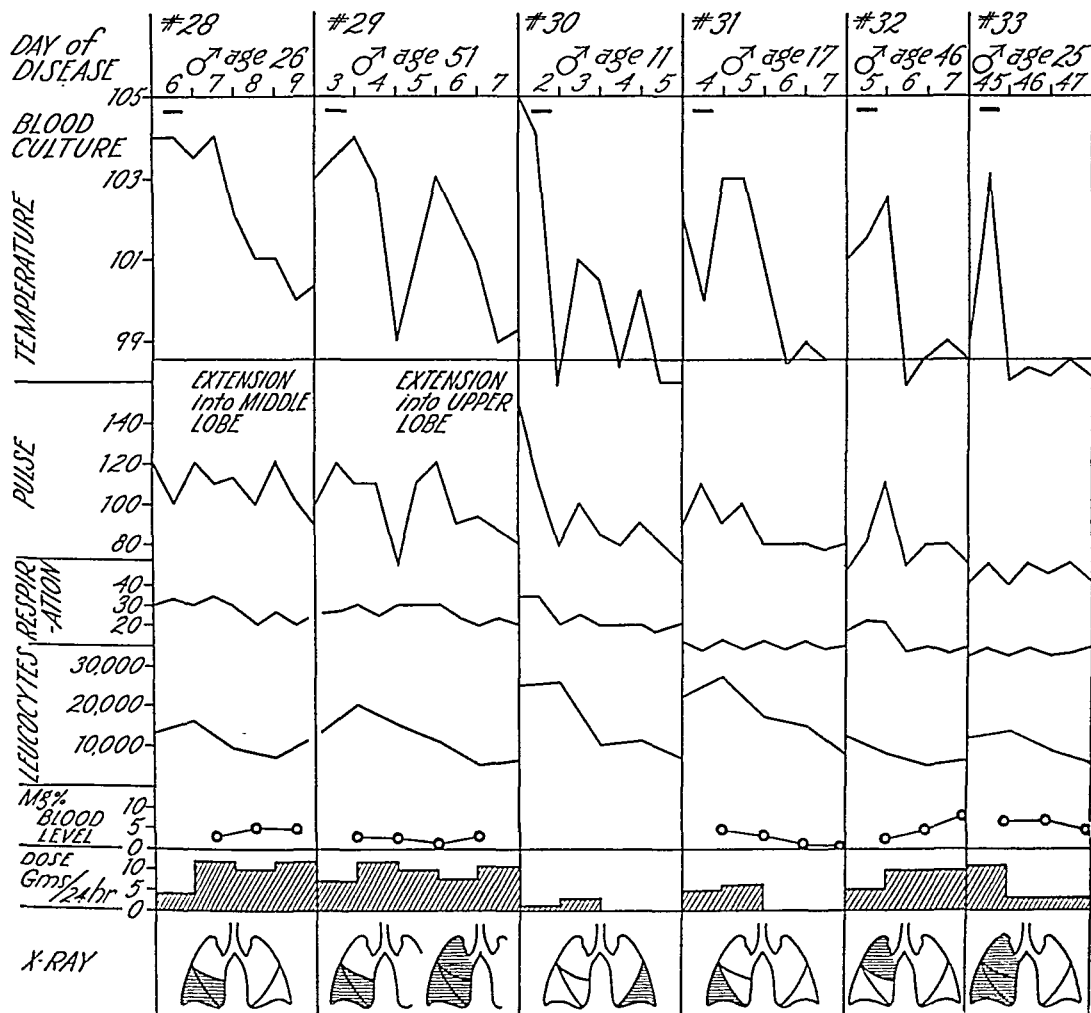


FIG. 5. Clinical summary of six patients with Type V infection.

One patient suffering from an active Type VII infection, Case 33 (figure 5), had had an empyema for 45 days before admission. An immediate response to sulfapyridine occurred (figure 5) before the fluid was aspirated from the pleural cavity. When the blood level of free sulfapyridine was 6 mg. per 100 c.c., its concentration in the fluid aspirated from the chest was 3 mg. per 100 c.c. Repeated aspirations with a large caliber needle were the only method necessary for adequate drainage.



## SUMMARY

(1) Fifty patients suffering from pneumococcic pneumonia have been treated with sulfapyridine, of whom three died. The mortality in patients receiving no specific therapy in the previous two years was 48 and 33 per cent. Seventeen of the patients were over 40 years of age; three or more days had elapsed since the onset of the disease in 23 patients; bacteremia occurred in eight patients; one lobe was consolidated in 16 patients, two lobes in 29 patients and three lobes in five patients. Empyema was observed in three patients and sterile effusion in three.

(2) No strict relationship was observed between the level of sulfapyridine in the blood, the amount administered, and the occurrence of toxic manifestations. The manifestations of toxicity were: (a) moderate to severe nausea and vomiting in about 80 per cent of the patients; (b) occasional leukopenia; (c) rare anemia; (d) hematuria.

(3) The response of the leukocytes was unpredictable, but in most cases paralleled the temperature curve. In fatal cases they may continue to rise in spite of high concentrations of the drug in the blood. Initial leukopenia does not necessarily contraindicate the use of sulfapyridine since the leukocytes may rise after its administration. It seemed wise to discontinue treatment in three patients because of increasing leukopenia.

(4) Specific antipneumococcus serum was employed in conjunction with drug therapy chiefly because of the occurrence of (a) leukopenia; (b) nausea and vomiting; (c) hematuria.

(5) One of eight patients with bacteremia died of pneumococcus endocarditis (Type XIV). Larger than usual doses of sulfapyridine were given these patients and the drug was continued longer because bacteremia recurred in one patient after early discontinuance.

(6) Empyema requiring surgical drainage occurred in two patients after sulfapyridine treatment. The concentration of free sulfapyridine in the pleural fluid was about half that in the blood. Sulfapyridine in the exudate may aid in preventing the growth of bacteria in it.

(7) Three patients died and in two of these the infecting organism was Type XIV. The concentration of free sulfapyridine in the blood was kept at high levels, but appeared powerless to arrest the infection. The third patient suffered from a Type V infection, which was controlled by the drug in spite of the fact that treatment was not begun until seven days after onset. Shock occurred on the eleventh day and the patient died a day later. An acute ulcer was found in the cardiac portion of the stomach.

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The ability of pneumonia to spread during a period of inadequate treatment with sulfapyridine was illustrated by Case 17 (figure 3). The drug was stopped because of leukopenia. Immune rabbit serum (100,000 units) was given with only transient effect. The leukocytes rose to 21,000 and more sulfapyridine was given following which a prompt fall in temperature was observed. Leukopenia again recurred. A second relapse occurred 13 days later with an increase of leukocytes. Sulfapyridine was again given and although the temperature fell to normal and physical examination indicated subsidence of the pneumonic process, the leukopenia recurred for the third time.

### LEUKOCYTES

The effect of sulfapyridine on the leukocyte count was unpredictable. In the majority of patients it paralleled the temperature curve, but there were numerous exceptions to the rule. In eight patients who received comparatively small doses of the drug (less than 30 gm.) the leukocyte count fell to about 3,000, but agranulocytosis did not occur in any of them.

The leukocytes did not decrease rapidly in all patients. In Case 5 the large amount of sulfapyridine given in the first five days produced only a slow decline. In the fatal cases, in spite of high concentrations of sulfapyridine, the leukocyte count continued to increase.

In those patients who had leukopenia on admission, Cases 12, 8 (figure 2), 27 (figure 4), administration of the drug resulted in an increase rather than decrease in the leukocyte count.

It is interesting that all patients with initial leukopenia had a high percentage of polymorphonuclear leukocytes and as the leukocyte count increased the percentage of polymorphonuclear cells decreased. Leukopenia apparently need not necessarily be considered a contraindication for the use of this drug when the etiological agent is the pneumococcus.

### RED BLOOD CELL COUNT AND HEMOGLOBIN

Blood counts and hemoglobin determinations were done on all patients at regular intervals during the period of administration of sulfapyridine, through the courtesy of Dr. Paul J. Fouts of the Lilly Laboratory for Clinical Research. Evidence of anemia which probably was caused by the drug was observed in two patients. In the first one, Case 16 (figure 3), a girl, aged 15, who was desperately ill with Type V pneumonia with bacteremia, 54 grams of sulfapyridine were given in a period of 13 days. The red blood cell count decreased from 4,000,000 with 84 per cent hemoglobin to 2,600,000 with 64 per cent hemoglobin and 8.6 per cent reticulocytes. The leukocytes declined from 10,000 to 4,500. After discontinuing the drug the red blood cell count returned to normal within two weeks without treatment.

The second example of anemia occurred in a patient, Case 49, with a Type III infection complicated by empyema. She received 84 grams of

# THE AMERICAN BOARD OF INTERNAL MEDICINE AFTER FOUR YEARS; ORGANIZATION, PURPOSES, AND THE EFFECTS OF SPECIAL BOARDS ON MEDICAL EDUCATION AND PRACTICE\*

By E. E. IRONS, F.A.C.P., *Chicago, Illinois*

WHEN the American Board of Internal Medicine was organized, many of us thought that if what we had in mind could influence favorably the quality of medical preparation and practice in perhaps ten or fifteen years, the effort would be well worth while. However, the effects on younger men entering medicine have been immediate and startling in scope.

In almost every large hospital many interns are now talking not about how soon they can get into practice, but about what more they can do, either by residencies, further basic science training or in positions of part time practice to qualify themselves to be better doctors. Many influences in medical education have been at work, but the operation of special boards has contributed much of the impetus to the advance in graduate medical education. You may be interested in hearing of the work of the American Board of Internal Medicine, whose organization was initiated and underwritten by the College, and of its present and future relation to graduate medical education as the Board and College conceive it.

## ORGANIZATION

The American College of Physicians through its Board of Regents on April 30, 1935, adopted a resolution for the establishment with the Section on the Practice of Medicine of the American Medical Association of an "American Board for the Certification of Internists." The Section on the Practice of Medicine adopted a similar resolution in June 1935, and a joint committee of nine members appointed by these two bodies met for preliminary organization in Philadelphia December 14, 1935. After approval by the Advisory Board the final organization was effected and articles of incorporation filed on February 28, 1936. Final approval of organization was given by the College, by the Council on Medical Education, and by the Section on Practice of Medicine at the annual meetings following. The first meeting of the Board was held on June 14, 1936, under the chairmanship of Dr. Walter L. Bierring. Membership on the Board as finally determined consists of five members from the College, and four from the Section on the Practice of Medicine.

Among the major problems of the Board were the establishment of a list of internists entitled to certification without examination, upon application

\* Read at the Cleveland meeting of the American College of Physicians April 1, 1940.

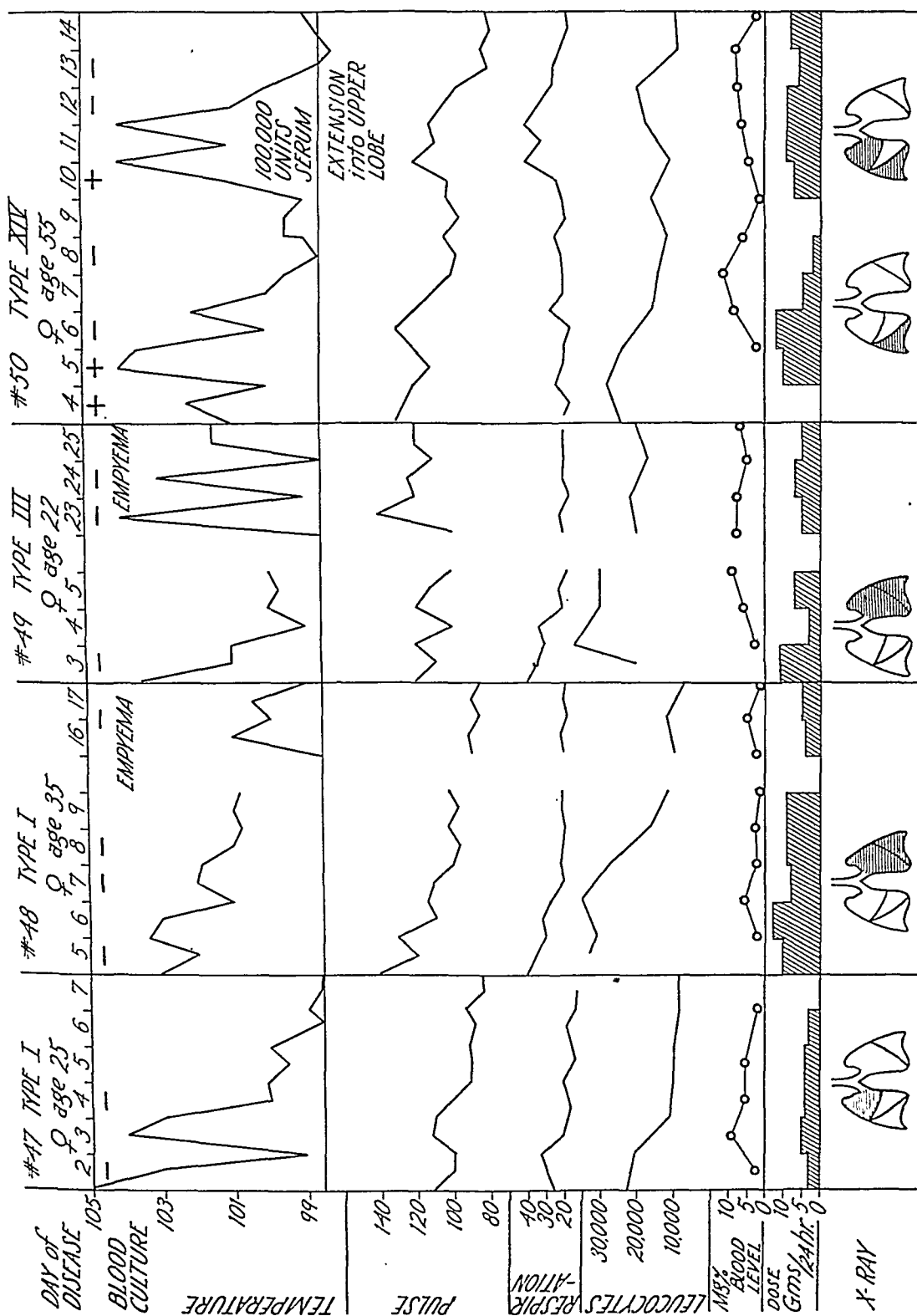


FIG. 8. Clinical summary of two patients with Type I, one patient with Type III and one with Type XIV.

Though often forgotten in these days, the economic laws of supply and demand are inexorable in medicine as in the production and marketing of corn. And in medicine, as they have proved in agriculture, attempts artificially to modify the operation of these laws can have only a temporary and often ultimately a deleterious effect.

The educational needs of these several levels differ just as the economic needs of communities differ. Neither can be supplied by general legislation. There is required individual level planning just as there is necessary economic regional planning.

At the moment, we are concerned with those who desire to qualify themselves especially in internal medicine. This group is comparatively small at present, when we consider the great body of physicians who prefer to engage in general practice, a field of action of much larger importance to medicine as a whole. It is perhaps not an idle hope that as the years go on, many of those who have elected first to acquire an understanding of medical problems in the school of practice may wish later to add to their store of knowledge from other sources. Medical experience in practice is essential to the attainment of full medical stature, but the rapid expansion of medicine whereby its borders touch on a multitude of ancillary subjects not recognized as important a few years ago, has complicated the problem of the young physician. He must exercise special care not to be drawn so far into the responsibilities of practice in his early years that he loses his facility in other technics just as necessary for his continued growth.

#### REQUIREMENTS OF THE BOARD

The requirements of the Board for admission to examination as outlined in the published brochure are designed as a guide to the type of preparation which the board believes will best fit the candidate for the examination, and much more important, will enable him to progress far, and to take a worthy part in the advances in medicine of the future.

A few quotations will illustrate the spirit and intent of these recommendations: "The American Board of Internal Medicine does not propose to establish fixed rules for the preliminary training of candidates for certification in this field. Broad general principles for training, however, may be outlined although such suggestions as are made must of necessity be subject to constant changes reflecting the dynamic nature of the specialty."

"A sound knowledge of physiology, biochemistry, pharmacology, anatomy, bacteriology and pathology as they apply to disease is essential for continued professional growth of the individual who practices internal medicine. Such knowledge may be acquired in a number of ways." These include residencies with adequate educational opportunities, graduate work in basic sciences closely integrated with clinical facilities, and service in well organized clinics or in preceptorships.

Residencies in well ordered hospitals afford continued clinical contacts and at the same time opportunity for the further acquirement of funda-

The longer the interval before treatment, the slower this resolution despite the fact that fever may disappear with equal celerity.

The complications attending the use of the drug were few and for the most part not serious except for vomiting and nausea. These occurred in most of the patients, but became important in less than a quarter of them. Anemia and hematuria were unusual.

The response of the leukocytes was unpredictable, although in many patients their number paralleled the temperature curve. The leukocytes continued to increase in our fatal cases in spite of high concentrations of free sulfapyridine in the blood. This may be of some prognostic significance. Our data (figures 2-4) do not indicate, as might have been expected, that leukopenia is a definite contraindication for the use of the drug. Indeed, the leukocytes rose from an initial low level after starting treatment in three patients. It seemed desirable to discontinue treatment because of increasing leukopenia in another three patients. It is interesting that all patients with initial leukopenia showed high percentages of polymorphonuclear leukocytes and that as the leukocytes increased in number their percentage decreased.

Too early withdrawal of the drug may be followed by spread of the pneumonic process. It has been our practice when temperature and pulse return to normal to reduce the dose to 5 grams a day and continue this for three days. Recrudescence is treated by raising the dose to 10 grams a day for 24 to 48 hours. It has been found to be a matter of the greatest importance to examine the patient with care when the fever has disappeared to be sure of resolution.

Bacteremia did not prove to be as serious a handicap in patients treated with sulfapyridine as is usual in patients receiving no specific therapy. One of eight patients died and this one had pneumococcic endocarditis.

We have found it desirable to employ antipneumococcus serum in a few patients in conjunction with the drug chiefly for two reasons, namely, nausea and vomiting and leukopenia. It appeared that we would have been seriously handicapped in our management of these cases had not serum been available.

Empyema developed under treatment in two patients, who later required surgical drainage. Of interest is the fact that fluid aspirated from the chest of a patient with a blood level of 6 mg. per 100 c.c. of free sulfapyridine, contained 3 mg. per 100 c.c. of the drug. It is possible that the relatively free diffusibility of sulfapyridine aids in bacteriostasis in exudates.

We are aware that excessively large doses of sulfapyridine in animals may lead to formation of concretions in the urinary tract. Further, renal damage might result from the clearance of such large amounts of a pyridine-containing drug. Actually no serious damage to the kidneys has been observed in our patients as measured by urea clearance and routine examination of urine specimens. Whether nuclei for future stones have been left in the urinary tract cannot be foretold.

tional examiners, near the time and place of the annual meetings of the College of Physicians and of the American Medical Association.

Papers are known by number only. The papers are read by members of the Board and failing or doubtful papers are read by two and if necessary by a third member. This has entailed the expenditure of much time and effort. The thought uppermost with the Board has been that of maintaining fairness, of a realization of what the result means to the candidate, and of maintaining a high standard of performance.

Certain clinical questions involving for example the interpretation of physical signs and symptoms in a case history have elicited answers, some right, some wrong. In giving a wrong answer the candidate may have taken the wrong turn at a critical point or misinterpreted the relative importance of facts as related in the question, and yet at the same time may have shown excellent ability in reasoning and in correlating his data as he understood them. On the other hand, a candidate may stumble on the right answer and yet show himself woefully weak in ability to correlate and interpret facts. The wrong answer may call for a better grade than the correct answer. I hasten to note, however, that the Board would not wish to put a premium on wrong answers.

Failures in examinations are directly attributable to inadequate preliminary training and insufficient experience. Some candidates who were refused admission to examination on these grounds were later admitted after two years further preparation and were successful in the examinations; other candidates whose records indicated what might be expected to be adequate training, were deficient both in factual information and in the ability to reason out clinical problems. In general the well trained candidate experienced but little difficulty.

Those who are inclined to regard some questions asked by the Board as too technical, and in the nature of catch questions, may forget that this is not an examination to test minimal standards for licensure but rather to ascertain the acquirement of the broad knowledge which may reasonably be expected of him who assumes to have a superior knowledge of the practice of medicine.

#### SPECIAL GROUPS IN INTERNAL MEDICINE

Until quite recently the multiple duties of the Board of Internal Medicine prevented its taking up the important matter of representation in the work of the Board of certain of the sub-specialties in internal medicine, such as cardiology, gastroenterology, tuberculosis, allergy, etc. Many of the leaders in these fields are already certificants of the Board, but they feel, and the Board agrees, that recognition should be given to these special sub-groups. The Board believes that all candidates in sub-specialties should have a broad foundation in internal medicine, and that therefore they should be prepared to pass the examination outlined in Parts I and II. In the practical examination the Board will invite representatives from lists nominated by the cor-

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of the Council on Medical Education. By June 1940 ten of thirteen special boards will have lists of approved residencies identical with those of the Council.

Recently a commission on Graduate Medical Education representing agencies concerned in medical education including Medical Schools, Hospitals and State Boards has completed a report which will be of value in indicating requirements and standards in this increasingly complex field.

The action of the Regents of the College in making certification by the American Board of Internal Medicine a prerequisite for promotion from associate to fellow in the College is a further evidence of the interest of the College in promoting medical scholarship and is a gracious recognition of the work of the Board.

In its arduous work the Board has been ably supported by the College, the Council on Medical Education and Hospitals, and by the American Medical Association. There are many fields of service in American medical life, of which we occupy only a small part. We wish to be of service to all, especially to that great body of general practitioners who carry the real load. Although we might sometimes like to think otherwise, men differ in tastes and ideas, in the type of their original mental equipment, and in their ability and willingness to work, sometimes for long periods without reward. Judgment as to his own special aptitudes for one or another kind of specialized work also plays a part in determining the ultimate field of activity and the attainments of the physician. The Board conceives its functions to include the encouragement of men to acquire a broad educational foundation both cultural and scientific, to reason carefully, to engage in long term planning, to work diligently, to the end that they may improve the quality of medical care of patients and contribute to a superior standard of American medical scholarship.

prior to July 1, 1937; the formulation of an advisory memorandum of recommended preparation for applicants for examination; plans for written and oral examinations. The preparation of the list of those certified without examination entailed an enormous amount of work, in which the Board availed itself of the invaluable advisory assistance of members of the Association of American Physicians. No doubt the Board has committed some errors of omission, but these have been unintentional, and in the main have occurred by reason of the inaccessibility of evidence. They have been in large part corrected.

Thus far 1800 have been certified without examination and 358 certified by examination.

### GRADUATE MEDICAL EDUCATION

Before passing to a more detailed consideration of the work of the Board, we may digress a moment to comment on the general problem of Graduate Medical Education as it affects the work of the Board. When the prospective doctor decides to enter the profession of medicine as a life work, he directs his premedical studies to comply with the entrance requirements of the medical school and then follows the prescribed medical curriculum and serves an internship, all in compliance with curricular and legal provisions. He then passes the examinations of a State Board or their equivalent and is admitted to practice. While he may do additional voluntary work in preparation, the larger part of his study has been necessary to comply with the demands of the police power of the State. In contrast to the undergraduate period, any further graduate study including preparation for board examinations is entirely voluntary. The content also of these graduate studies is optional, although experience shows that certain types of study are likely to fit the needs of most candidates and are therefore recommended. As in any other field of education, there will be dissimilar views, diverse types of intellectual fitness, and varying degrees of the will toward scholarship. All that graduate medical education can or should attempt to do is to furnish guidance and opportunity. Compulsion and regimentation have no place here. Democracy in medicine like democracy in political fields depends on the acceptance of personal responsibility by the individual. Initiative and sense of responsibility must be stimulated in the individual if we are to avoid the dangers and stunting effects of paternalism.

With the rapid expansion of the field of medicine it has become no longer possible for one man to acquire even a moderate knowledge of the entire field, and the necessary division into special fields has resulted in an ever increasing number of legitimate subdivisions, expertness in each of which requires a life time of experience.

The medical work of the world must be done by many hands and at many levels. Work at each level is well worth while, and offers abundant satisfactions to him who does his job well. Nor should there be any attempt to dictate how many men should be allotted to one or another group or level.

19,950 per cubic millimeter. The urine had a faint trace of bile, and urobilinogen was present in a dilution of 1 to 20 but absent in a dilution of 1 to 40. On December 17 he complained of pain in the right upper quadrant of the abdomen. His physician found that the temperature had remained under 100° F., and that the face lesion was definitely improved, but that the icterus of the sclerae was deeper and seemed to be present also in the skin, and that there was mild percussion and palpation tenderness in the right upper quadrant of the abdomen. Hospitalization was advised and the patient was admitted to the medical service of Dr. Henry Schumer on December 17 at 4 p.m.

At this time he appeared subacutely ill, with a rectal temperature of 99.2° F. There was erythema and moderate desquamation of the skin of the forehead and cheeks, with slight swelling. The sclerae were icteric and there was mild icterus of the remainder of the body. The mucous membranes of the hard palate and posterior pharynx exhibited a yellowish tinge. The liver was not palpable. The remainder of the physical examination was normal.

*Course:* The patient was started on a continuous infusion of 5 per cent glucose in physiologically normal saline containing 50 mg. of vitamin B<sub>1</sub> per 1000 c.c. of fluid, and had received 1300 c.c. when this therapy was discontinued the following day. It was replaced by a high-carbohydrate, low-fat diet. The blood chemistry on December 18 revealed glucose of 134 mg. per cent, urea nitrogen 23.1 mg. per cent, uric acid 4 mg. per cent, cholesterol 217.4 mg. per cent of which 114.4 mg. per cent or 53 per cent of the total were esters; the total protein was 5.62 grams per cent. The stool was faintly positive for bile but was negative for blood. The hippuric acid test showed 2.4 grams of benzoic acid recovered as hippuric acid in five hours (normal is 3 grams or more). The urine was amber, acid with a specific gravity of 1.018; sugar, albumin and acetone were absent, and the microscopic examination was negative. The admission icteric index was not determined due to the loss of the blood sample.

The jaundice was clinically absent by December 20, at which time the icteric index was 7.0 and the Van den Bergh reaction was direct delayed with a serum bilirubin of 0.5 mg. per 100 cubic centimeters. Urobilinogen was present in the urine in a 1 to 80 dilution and there was a faint trace of bile in the urine. A blood study on December 19 showed a hemoglobin of 50 per cent Sahli (7.3 gm.) with 2,820,000 red cells, total leukocytes 11,300, with a differential of 66 neutrophils, 1 basophile, 10 band forms, 20 lymphocytes and 3 monocytes. The morphology of the red blood cells was normal. The blood sulfanilamide concentration on December 18 was less than 0.5 mg. per cent. The urine on December 19 was red and contained numerous red cells; urines repeated on six occasions showed red cells present five times, ranging from 2 to 3 per high power field up to "numerous." On December 21 the blood hemoglobin was 48 per cent Sahli (7 gm.) with 2,420,000 red cells per cubic millimeter. On December 22 the urobilinogen in the urine decreased to positive in a 1 to 30 dilution with a very faint trace of bile remaining. On December 23 the prothrombin time (Smith's method) was 100 per cent of normal. The fragility of the red cells was determined December 23 and revealed hemolysis to begin at 0.42 per cent and to be complete at 0.30 per cent. On December 24 the hemoglobin was again 48 per cent Sahli (7 gm.) and the red cells were 2,770,000 per cubic millimeter.

The patient was given a transfusion of 500 c.c. of citrated blood on December 25. Following this the hemoglobin and red cells increased; on December 26 the hemoglobin was 66 per cent Sahli (9.6 gm.) with 3,820,000 red cells and leukocytes 7,900 per cubic millimeter. The differential count showed 73 neutrophils, 7 band forms, 12 lymphocytes, 6 monocytes, 1 eosinophile and 1 Turck cell per hundred cells.

The icteric index on December 28, the day before discharge, was 10.3, the Van den Bergh reaction was direct delayed and there was 1.0 mg. per cent of serum bilirubin. The hippuric acid test on this day showed 3.4 grams of benzoic acid excreted

mental basic technics under the guidance and inspiration of older men. Such residencies while perhaps safer for the average younger man who is entering the critical first five years of his medical career, are by no means the only avenues by which he may travel toward the medical scholastic goal. He may already have a definite prospective goal of accomplishment in mind, and to this end may require one or more years of special basic preparation, or, as is perhaps more likely, he may still be searching for the precise line along which he shall go. Medicine is expanding rapidly and his final decision may have to wait. In the meantime, a careful choice of his medical associations, perhaps in the nature of a preceptorship or in a clinic with a practical but scholarly atmosphere will fit his needs. There is no one road, and if there were such, to require all men to travel it would dwarf the growth of many a choice spirit destined in freer surroundings to a high place in medicine.

"The mere factual knowledge of medicine and its basic sciences is not sufficient. The candidate must have training in their use." This implies practical experience, with emphasis on the concepts of the experimental method, under the guidance of older men who bring to their clinical problems ripe knowledge and clinical judgment.

"Although it is required that at least five years must elapse between the termination of the first intern year and the date when the candidate is eligible to take the examination, a longer period is advisable."

For many candidates an examination which, taken after the minimal five years training would be an anxious period, would, taken after seven or eight years, be an interesting and perhaps even an enjoyable experience.

"Time and training are but a means to the end of acquiring a broadness and depth of knowledge of internal medicine." "The responsibility of acquiring the knowledge as best he may rests with the candidate; while the responsibility of maintaining the standard of knowledge required for certification devolves upon the Board."

It may again be noted that these suggestions are advisory only. No doubt some candidates will appear with quite different but nevertheless adequate preparation. We are reminded that Robert Koch might have had difficulty in qualifying before a board in his time. Emphasis should be on standards rather than on standardization. A reasonable amount of organization and definition is required, however, to make realization of standards possible.

### THE EXAMINATION

The examination consists of a written Part I which is held simultaneously in different regions of the United States and Canada on the third Monday of February and October of each year.

Section A includes questions in the basic sciences as related to internal medicine; Section B consists of questions in general internal medicine. Candidates successful in Part I are eligible for the practical or clinical examination (Part II) which is conducted by members of the board assisted by addi-

CHART 1  
Case 1

	12-16-39	12-18-39	12-19-39	12-20-39	12-21-39	12-22-39	12-23-39	12-24-39	12-25-39	12-26-39	12-28-39	12-29-39	1-8-40	1-22-40
BLOOD														
Hemoglobin (Sahli)	70%		50%		48%			48%		66%	75%		76%	90%
Hemoglobin grams	10.1		7.3		7.0			7.0		9.6	10.8		10.9	13.1
RBC (millions per cu.mm.)	4.4		2.82		2.42			2.77		3.48	3.82		3.9	4.71
WBC per cu.mm.	19,950		11,300								7,900		6,700	9,500
Polys per 100 cells			66								73		60	51
Bands per 100 cells			10								7		2	0
Lymphs per 100 cells			20								12		31	40
Reticulocytes													0.9%	
Fragility										5.2%				1.4%
Icteric index														
Serum bilirubin mg. %														
Van den Bergh				7.0										
				0.5										
Prothrombin time (Smith's method)				Direct										
Chemistry				Delayed										
Urea nitrogen (mg. %)		23.1												
Uric acid (mg. %)		4.0										16.3		
Cholesterol (mg. %)		217.4										3.1		
Cholesterol esters (mg. %)		114.4												
Total protein gm. %		5.62												
Sulfanilamide conc. (mg. %)		<0.5										6.9		
URINE														
Appearance		Amber	Red	Yellow	Cloudy Amber	Amber				Straw		Amber		Yellow
Urobilinogen (highest positive dilution)	1:20			1:80		1:30				1:30				1:20
Bile				Faint trace		Very faint trace				Absent				
Microscopic		Neg.	Num-erous red cells	2-3 red cells	Num-erous red cells	Occ. RBC						2-3 red cells		Neg.
HIPPURIC ACID SYNTHESIS														
Total amount excreted in 5 hours calculated as benzoic acid gm.		2.4								3.4				

responding sub-specialty to sit with the Board, and examine candidates in subjects of the special field. The certificate will bear an appropriate notation of proficiency in the sub-specialty.

### THE RELATION OF SPECIAL BOARDS TO THE GENERAL PROBLEM OF MEDICAL EDUCATION

The immediate field of the Board of Internal Medicine is a relatively limited one, but its problems are similar to those of other boards, and its influence in raising standards is naturally correlated with that of other agencies in graduate medical education. In time it will assist in raising the level of under-graduate medical education by setting standards of scholarship toward which the young student may strive.

Special boards may at times take too narrow a view of their own specialties. Their function is not to tell a man what he should do, but rather to suggest how he may do it better. Special fields of medicine are not closed boxes. Their borders are better defined only in general terms, and attainment in each field stems from a necessary broad knowledge of the fundamentals of medicine. An internist should not hesitate to look at a retina, and an expert gynecologist should be qualified to deal with whatever he finds on opening the abdomen. Those directing the activities of special boards would do well to avoid jurisdictional quibbles and be guided rather by what is best for American Medicine.

Some hospitals have considered making certification by special boards a prerequisite for staff appointments. This is of course a question of hospital policy, with which the boards have no concern. The acquirement of certification is voluntary, and the Boards are interested only in standards. The hospital may wish to avail itself in many instances of the judgment of the Boards, but at the present time there are many men, especially of the older group, who are well prepared, but who have not wished to apply for certification. The conditions and needs peculiar to each community should be considered in the determination of local policy.

### COÖPERATION WITH OTHER AGENCIES

Encouraging progress has been made in establishing active coöperation between the agencies charged with the several phases of medical education. The quality of residencies and similar graduate educational opportunities concerns the American College of Physicians, the Council on Medical Education and the Board of Internal Medicine. The Council on Medical Education and Hospitals has extended its field from that of undergraduate medical schools and internships, in which it has accomplished so much in the past 35 years, to now include hospital activities in the graduate field. During the past year a coöperative committee of two representatives of each group has been established to secure the necessary data for ascertaining the quality of residencies, utilizing the organization already operating under the direction

On April 4 the red blood cells numbered 2,360,000 per cubic millimeter, with 50 per cent hemoglobin, Sahli (7.2 gm.); the volume index was 0.9 and the morphology of the red blood cells was normal. The total leukocyte count was 14,200 per cubic millimeter, with a differential count of 78 neutrophils, 3 band forms, 7 lymphocytes, 10 monocytes, 1 young form and 1 eosinophile. The hippuric acid synthesis test showed 1.96 grams of benzoic acid excreted as hippuric acid, indicating impairment of liver function.

The anemia persisted despite active attempts at regeneration as evidenced by a reticulocyte count of 8 per cent on April 5, with red cells 1,980,000 and 42 per cent hemoglobin, Sahli (6 gm.); the white blood cell count then was 12,100 per cubic millimeter. The blood picture remained about the same the next day (April 6), the hemoglobin being 41 per cent, Sahli (5.9 gm.), with 2,020,000 erythrocytes. The sulfanilamide concentration in the blood was determined to be 0.6 mg. per cent.

The jaundice cleared rapidly, the icteric index on April 5 falling to 7.3 while the Van den Bergh reaction was now delayed direct with 0.6 unit of serum bilirubin per 100 c.c. of blood. The stool was negative for blood and bile. Repetition of the bromsulphalein test on April 8 again showed no dye retained in the blood serum after 30 minutes. The blood glucose was 87.8 mg. per cent; the urea nitrogen had decreased to 16.7 mg. per cent; the uric acid was 3.3 mg. per cent and the creatinine 1.23 mg. per cent. The icteric index was only 6.2 and the Van den Bergh reaction again direct delayed with 0.5 unit of serum bilirubin per 100 cubic centimeters.

On April 9 the erythrocytes had increased to 2,920,000, the hemoglobin to 49 per cent, Sahli (7.2 gm.) and reticulocytes to 11.4 per cent. There were 18,800 white blood cells per cubic millimeter, with 58 neutrophils, 7 band forms, 4 young forms, 2 myelocytes, 17 lymphocytes, 2 eosinophiles, 2 basophiles and 2 Turck cells per hundred cells. The urine at this time was negative for bile and the urobilinogen had fallen to positive in 1:10 dilution. The normal resistance of the red cells to hypotonic saline was confirmed by repetition of the fragility test on April 10, at which time hemolysis was noted to begin at 0.40 per cent and to be completed at 0.28 per cent.

Slow improvement of the blood picture continued. On April 12 the red blood cells numbered 3,360,000 and the leukocyte count was 10,700, with a differential of 68 neutrophils, 1 band form, 23 lymphocytes, 6 monocytes and 2 eosinophiles. On April 15 the red cell count was the same, the hemoglobin was 68 per cent Sahli (9.9 gm.), and the reticulocyte count had fallen to 1.2 per cent; the leukocyte count was 12,000, with about the same differential.

The hippuric acid synthesis test was performed again on April 17 and showed 2.39 grams of benzoic acid excreted as hippuric acid, indicating an improvement in liver function.

During the remainder of his stay the patient felt better, and visible jaundice disappeared completely April 10. The patient was discharged improved on April 18.

On May 26, five weeks after discharge, the hemoglobin was 92 per cent Sahli (13.3 gm.), the red blood cells 4,310,000 and the white cells 9,850, with a normal differential.

The laboratory findings are summarized in the accompanying chart (chart 2) and graph (figure 1).

#### COMMENT

This patient presented many features similar to those of Case 1. There was an early onset of jaundice, following mild gastrointestinal symptoms. This occurred 60 hours after starting sulfanilamide therapy and 24 hours after administration of the drug was discontinued. The total dose given was 110 grains (7.3 gm.). At the same time a moderately severe anemia developed. This was

# CASE REPORTS

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## THE COEXISTENCE OF TOXIC HEPATITIS, ACUTE HEMOLYTIC ANEMIA AND RENAL DAMAGE FOLLOWING SULFANILAMIDE THERAPY; REPORT OF TWO CASES \*

By MAXWELL SPRING, M.D., and ISIDOR BERNSTEIN, M.D., *Bronx, New York*

IN 1937 Harvey and Janeway<sup>1</sup> first described acute hemolytic anemia as a toxic manifestation of sulfanilamide therapy. They presented three cases in adults. Shortly thereafter Kohn<sup>2</sup> and Willis<sup>3</sup> each presented a case in an infant. Wood<sup>4</sup> studied 522 patients, 144 children and 378 adults, receiving sulfanilamide and found that 21 developed acute anemia. Of these, 12 or 8.3 per cent were children, and nine or 2.4 per cent were adults. Long, Bliss and Feinstone<sup>5</sup> in their study of 307 adults and 101 children found the incidence 2.9 per cent and 8.9 per cent respectively. In 1938 Bannick, Brown and Foster<sup>6</sup> first mentioned hepatitis as another evidence of sulfanilamide toxicity. That same year Garvin<sup>7</sup> presented five cases as examples of this manifestation. However, in 1937 Hageman and Blake,<sup>8</sup> in describing a febrile reaction to sulfanilamide, had presented one case which showed a toxic hepatitis, but had not pointed this out as a reaction to sulfanilamide. The combination of toxic hepatitis and acute hemolytic anemia has not hitherto been described as a complication of sulfanilamide administration, with the possible exception of an unproved case by Garvin.<sup>7</sup> Furthermore, Ottenberg<sup>9</sup> noted that kidney damage is not mentioned in the literature as one of the toxic manifestations of sulfanilamide and records one case of marked albuminuria; the urine in his case also showed a few red blood cells on two occasions. He also described two cases of marked renal insufficiency in association with marked hemolytic anemia, hemoglobinuria and jaundice. The following two cases are examples of the coexistence of these toxic effects.

### CASE REPORTS

*Case 1.* A 55-year-old dress operator was first seen by his physician at noon on December 15, 1939, because of fever, chills and redness and swelling of his face. His temperature was 105.2° F. and he was found to have a facial erysipelas for which he was given sulfanilamide 15 grains, with sodium bicarbonate, every three hours. During the night he vomited and had diarrhea. He was seen at noon the following day, December 16, at which time the temperature had fallen to 99.6° F., the face lesion was the same, and the sclerae were faintly yellow. The sulfanilamide was immediately discontinued, the patient having had a total of 70 grains (60 grains on December 15 and 10 grains on December 16). At this time the hemoglobin was 70 per cent Sahli (10.1 gm.), the red blood cells were 4,400,000 and the white blood cells

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From the Medical Services of Dr. Henry Schumer and Dr. Emil Koffler, The Bronx Hospital, Bronx, New York.

We are indebted to Dr. Henry Schumer and Dr. Emil Koffler for permission to report these cases.



CHART II—Continued

	3-31-40	4-2-40			4-3-40	4-4-40	4-5	4-6	4-8	4-9	4-10	4-12	4-15	4-17	5-26
		Noon	10 p.m.	11 p.m.											
URINE															
Appearance			Brown	Transfusion—500 c.c. Blood					Straw	1:10			Amber		
Urobilinogen (highest positive dilution)			1+						Trace				Neg.		
Bile			Occ. WBC and gran. casts						Occ. RBC				Neg.		
Albumin															
Microscopic															
Spectroscopic for Hgb.															
HiPPURIC ACID SYNTHESIS															
Total amount excreted in 5 hours calculated as benzoic acid (gm.)						1.96								2.39	
BRONSULPHALEIN															
Retained in blood after 30 minutes					None				None						

as hippuric acid in five hours. Urobilinogen was present in a dilution of 1 to 30 and bile was absent from the urine.

The morning of the day of discharge the urea nitrogen was found to have decreased to 16.3 mg. per cent, the uric acid to 3.1 mg. per cent, and the total protein to have risen to 6.9 grams per cent.

The temperature remained normal throughout the duration of hospitalization. The facial lesion disappeared by December 22. On December 29 the patient was discharged, much improved.

The patient returned January 8, 1940, ten days after discharge, for a blood study. At this time his hemoglobin was 76 per cent Sahli (10.9 gm.), the red cells were 3,900,000 and the total leukocytes 6,700 per cubic millimeter. The differential count showed 60 neutrophils, 2 band forms, 5 eosinophiles, 1 basophile, 31 lymphocytes and 1 monocyte per hundred cells. The reticulated erythrocyte count was 0.9 per cent.

He returned again on January 22, 1940, at which time his hemoglobin was 90 per cent Sahli (13 gm.), the red cells were 4,710,000 and the white cells 9,500 per cubic millimeter, with normal differential count and reticulocytes of 1.4 per cent. The urine was entirely normal and urobilinogen present in a 1 to 20 dilution.

The laboratory findings are summarized in the accompanying chart.

#### COMMENT

The case presented has several features of interest. About 12 hours after therapy was started early toxic symptoms in the form of vomiting and diarrhea were noted. Within 24 hours, after 4.6 grams of the drug had been taken, jaundice was noted, and this progressed. At this time a blood count revealed a mild anemia and a faint trace of bile with normal urobilinogen in the urine. In view of the urinary findings, the jaundice, and the absence of hemolysis of red cells a toxic hepatitis must have been present at this stage. This was borne out by the pain and tenderness in the right upper quadrant, the diminished hippuric acid excretion and the low serum protein concentration; it was further confirmed by the return to normal of these findings by the time of discharge. The hepatitis was of mild degree since the jaundice cleared in five days, though the urine contained bile for some days later. The hepatitis was probably prolonged by the anoxia consequent upon the subsequently developed hemolytic anemia which reached its maximum five days after sulfanilamide was discontinued. In spite of the marked and rapid hemolysis there was no rise in temperature, only a slight leukocytosis and polynucleosis, and no change in the morphology of the red cells, features which have been considered as pathognomonic of acute anemia due to sulfanilamide (*vide infra*). The anemia responded dramatically to transfusion and one month later the blood count was normal.

The elevated urea nitrogen, which returned to normal by the time the patient was discharged, and the repeated presence of red cells in the urine noted on microscopic examination may have been due to some renal irritation or damage. The grossly red urine which was found at the height of the hemolytic process may have been due to hemoglobinuria, though no spectroscopic examination was done. Whether the kidney injury in the present case was due to sulfanilamide per se or to the presence of bile in the blood cannot be decided.

*Case 2.* A 30 year old white male was admitted to the medical service of Dr. Emil Koffler on April 2, 1940, because of marked painless jaundice which had begun the day before admission. The patient became ill on March 30, 1940, with a sore throat, generalized aches and pains and temperature of 105.5° F. His physician

peared one week after admission. The blood picture returned to normal five weeks after discharge and eight weeks after the onset of the illness.

### DISCUSSION

There have been described two types of anemia resulting from sulfanilamide therapy, the acute hemolytic and the "slow" or chronic forms. The latter was first described by Jennings and Southwell-Sander.<sup>10</sup> In this type of anemia, the fall of hemoglobin is slow and the maximum is reached in two to four weeks after therapy is started. There is no accompanying bilirubinemia, though increase in the reticulocytes above normal is the rule after the hemoglobin begins to fall. In none of the three cases they presented was icterus present, though in two of them the anemia was quite severe.

The other form, the acute hemolytic anemia, has the following features<sup>3, 11</sup>: (1) A rapidly progressive anemia coming on within three to five days following the onset of drug administration. The hemoglobin, however, begins to fall between 24 and 72 hours after therapy is started. Wood<sup>4</sup> found the anemia to occur only in febrile patients and to reach its maximum between the third and seventh days and usually on the fifth day. The hemoglobin may decline to levels of 30 to 40 per cent of normal during this process. This decline in red blood cells is accompanied by anisocytosis, pallor, many nucleated erythrocytes and reticulocytosis. (2) A polymorphonuclear leukocytosis which varies between 20,000 and 87,000 or more white blood cells per cubic millimeter which on smear exhibit many immature myelocytes. (3) Jaundice and signs of diminished hepatic function in some cases. (4) Prompt recovery following withdrawal of the drug, the use of blood transfusions and forcing fluids to 3000 cubic centimeters a day. (5) A definite rise in temperature during the anemic phase; this manifestation is more common in children than in adults.<sup>12</sup>

Early recognition of the condition may not prevent the progression of the anemia since sulfanilamide may continue to act for as long as 48 hours after its discontinuance. The use of the drug at some later date may cause a recurrence of the acute anemia.

Hepatitis may be mild or severe. The mild cases clear up rapidly after the drug is stopped. The severe cases may go on to acute yellow atrophy and death. As with the anemia, the hepatitis may progress in spite of the discontinuance of the drug, as illustrated by two of the cases presented by Garvin.<sup>7</sup> The symptoms and signs are anorexia, epigastric distress, nausea, at times vomiting, and pain and tenderness in the right upper quadrant of the abdomen, jaundice, enlarged tender liver (in mild cases there may be no enlargement), hyperbilirubinemia, urobilinuria, biluria and decreased hepatic function.

The problem of jaundice is an interesting one. Jaundice may be caused by the destruction of red blood cells, obstruction of the bile passages, or damage to the liver cells by toxic agents or infection. In any given case two or all three factors frequently exist. Skin icterus sets in only 24 hours after the onset of bilirubinemia when the bilirubin reaches a concentration of 1 in 80,000 in the blood. When the blood concentration reaches 1 in 50,000 bile appears in the urine.<sup>13</sup> Hemolytic bilirubin does not pass into the urine unless the concentration becomes very high. Indeed, Van den Bergh<sup>13</sup> and Rich<sup>14</sup> are of the opinion that bilirubin of pure hemolytic jaundice never appears in the urine, the presence of bile in the urine indicating that liver damage has been superadded.

found an acute pharyngitis for which he prescribed sulfanilamide. The drug was administered for the first time at 10 p.m. of that evening (March 30), a total of 90 grains being given between March 30 and March 31. The temperature the evening of March 31 was 100.5° F., and the patient felt much improved. A blood count on March 31 showed 4,500,000 red blood cells, with a hemoglobin of 85 per cent Sahli (12.3 gm.) and 28,000 white blood cells, with a differential of 90 neutrophils, 4 band forms and 6 lymphocytes. Twenty grains more of sulfanilamide were administered, the last dose being given at noon of April 1, bringing the total amount to 110 grains. He continued to feel improved except for slight nausea, occasional abdominal cramps and five loose bowel movements on April 1. The stools were black (the patient had been receiving oral iron medication since April 1) and his urine was dark brown in color. The patient was seen by his physician on April 1 at 10 p.m., at which time no jaundice was evident. On April 2 the family of the patient noticed that he was jaundiced; the physician confirmed this observation. At noon of April 2 a blood count revealed the hemoglobin to be 55 per cent Sahli (8.0 gm.), red blood cells 3,900,000, leukocytes 20,800; with a differential count of 76 neutrophils, 2 band forms, 16 lymphocytes, 5 monocytes and 1 eosinophile. Fifty cubic centimeters of a 50 per cent solution of glucose were given intravenously, following which he had a chill and his temperature rose to 103.6° F. The patient was advised to enter the hospital and was admitted at 5 p.m.

On admission the patient appeared markedly icteric; his temperature was 102° F., pulse 110 per minute and respirations 24 per minute. The sclerae were jaundiced. The only other significant findings were an injected pharynx and a liver edge palpable one finger below the right costal margin. The urine was brown and contained albumin one plus and occasional white cells and granular casts. A blood study at this time (10 p.m.) showed 2,260,000 red blood cells per cubic millimeter with 50 per cent hemoglobin Sahli (7.2 gm.); the total leukocytes numbered 49,300 per cubic millimeter, with 82 neutrophils, 11 band forms, 4 lymphocytes and 3 monocytes per hundred cells. The smear showed occasional nucleated red blood cells, anisocytosis and some central achromia. The icteric index was 68.0 and the Van den Bergh reaction immediate direct with 6.2 units of serum bilirubin per 100 c.c. of blood. Blood cholesterol was 166.2 mg. with 108.0 mg. per cent (65 per cent of total) as esters. The blood glucose was 97.6, urea nitrogen 24.4, non-protein nitrogen 53.6, uric acid 3.9 and creatinine 1.15 (all in milligrams per cent). The blood Wassermann and Kahn tests were negative.

At 11 p.m. of the day of admission the patient received a transfusion of 500 c.c. of citrated blood. He was placed on a high-carbohydrate diet. His temperature fell to 99.2° F. the next morning and then rose to 100.4° F., remaining at about 100 degrees until the sixth day of hospitalization after which it was normal until the time of discharge.

On April 3, the day after admission, the urine showed albumin 2 plus and occasional red cells, white cells and casts; it was negative for bile but was positive for urobilinogen up to 1:50 dilution. The benzidine test on the urine was 2 plus; spectroscopic examination for hemoglobin was negative. A blood study revealed reticulated erythrocytes 0.2 per cent, 190,000 platelets per cubic millimeter, bleeding time 2 minutes, coagulation time 4 minutes, clot retraction time 6 hours and prothrombin time 100 per cent of normal (Smith's method). An erythrocyte fragility test showed hemolysis to begin at 0.38 per cent and to be complete at 0.30 per cent. The sedimentation rate (Wintrobe method) was 16 millimeters at the end of one hour. The icteric index had fallen to 46.0 and the serum bilirubin to 4.5 units per 100 c.c. of blood; the Van den Bergh reaction remained immediate direct. The bromsulphalein test showed no dye retained in the blood serum after 30 minutes.

Urine examinations on April 4 and 8 showed traces of albumin and occasional casts; two subsequent urine examinations were normal.

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## ACUTE HEMOLYTIC ANEMIA, HEMOGLOBINURIA AND UREMIA FOLLOWING SULFANILAMIDE\*

By GORDON B. MYERS, M.D., F.A.C.P., and JACK ROM, M.D., *Detroit, Michigan*

WHILE acute hemolytic anemia is a fairly common complication of sulfanilamide therapy and has been carefully studied by numerous workers,<sup>1, 2, 3</sup> massive hemoglobinuria is relatively rare and has received little attention. Among 21 cases of sulfanilamide hemolytic anemia reported by Wood,<sup>3</sup> free hemoglobin was found in the urine in only one instance. Bohlman,<sup>4</sup> in discussing the toxic manifestations of sulfanilamide, referred to a personal communication from Janeway, who had had one case with hemolytic anemia, hemoglobinuria and uremia. In five other cases of sulfanilamide hemolytic anemia, reported in three different papers,<sup>5, 6, 7</sup> hemoglobinuria was noted as an incidental finding, but no mention was made of nitrogen retention.

\* Received for publication December 7, 1939.

From the Medical Department of Wayne University College of Medicine and City of Detroit Receiving Hospital.



TABLE I  
Course

Day	Date	Sulfanilamide grains	NaHCO <sub>3</sub> grains	Transfusions c.c.	Fluids		Blood						Urine																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								
					Intake c.c.	Output c.c.	Hb. G/100 c.c.	RBC	WBC	Ict. Ind.	Sulf. mg. %	Urea mg. %	CO <sub>2</sub> comb. power vol. %	PH	Sp. G.	Alb.	RBC	Free Hb.	Urobilinogen																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
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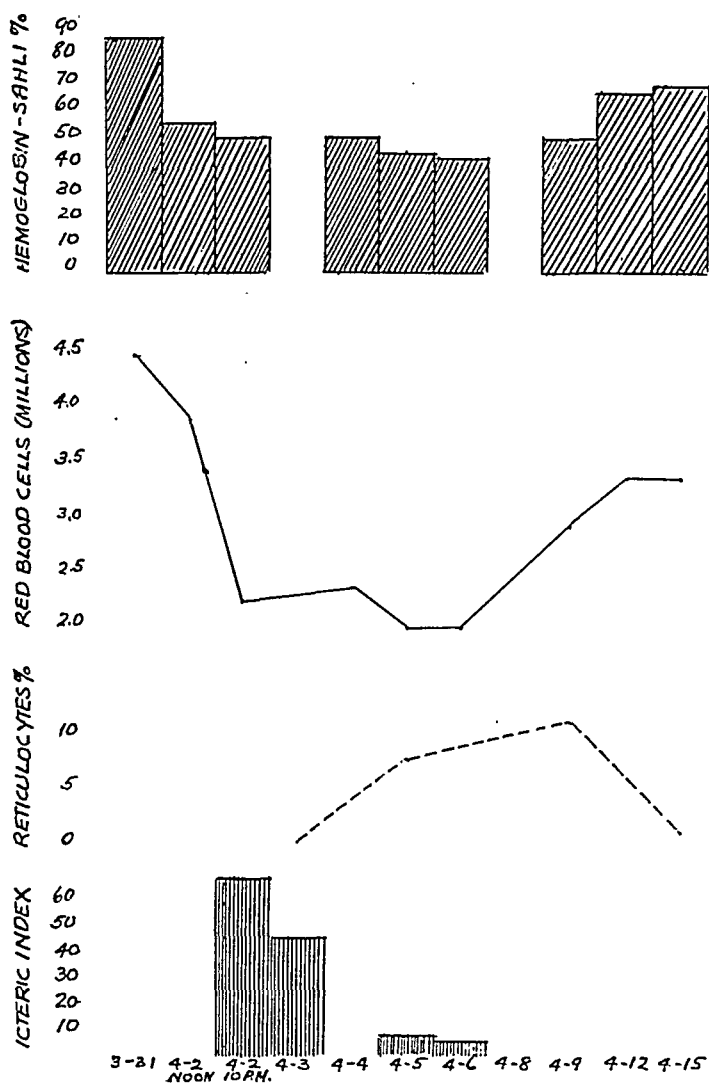


FIG. 1. Case 2. Showing time relationship of fall in hemoglobin and red blood cells to rise in icteric index and reticulocytes.

due to hemolysis of the red cells as shown by the progressive fall in erythrocytes and hemoglobin with marked reticulocytosis. The anemia continued in spite of transfusion, reaching its maximum on April 6, the fourth day of hospitalization. In contrast to the previous case, there was a rise in temperature, a marked leukocytosis, a polynucleosis, and alterations in the morphology of the red cells. Furthermore, there was only a slight response to the transfusion whereas in the first case a dramatic improvement occurred. Evidence of hepatitis (regurgitation jaundice) was present in this case also, as shown by the presence of clinical jaundice, an immediate direct Van den Bergh reaction, increased urobilinogen in the urine, and diminished hippuric acid synthesis, which later improved.

In this case, too, kidney damage was present and was more marked than in the first case. Urinary findings included albumin up to 2 plus, occasional red blood cells and granular casts while blood chemistry studies revealed elevations of urea nitrogen and non-protein nitrogen. Evidence of renal damage disap-



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## ACUTE TOXIC NECROSIS OF THE LIVER FOLLOWING THE USE OF SULFANILAMIDE\*

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THIS case is being reported because of the rarity of such severe liver damage following the use of this drug and to emphasize the importance of close observation of every patient receiving sulfanilamide or closely allied drugs.

### CASE REPORT

The patient was a white man, 46 years of age. The family and personal past history were without record of value. During the summer of 1938 he had complained of increasing nervousness and the presence of a small lump in the midline of the neck. He consulted his doctor who noted that his pulse varied between 87 and 105. The cardiac rhythm was regular. A basal metabolism test was ordered and reported to be plus 25 per cent. Blood cholesterol was found to be 125 mg. per cent. Urinalysis showed no abnormalities. A blood count showed erythrocytes 4,490,000; leukocytes 7,350; hemoglobin 74 per cent (Newcomer), 12.5 grams. A differential count of the leukocytes showed in each 100 white blood cells: Eosinophiles 1; metamyelocytes II 6; mature neutrophiles 60; lymphocytes 24; monocytes 9.

A clinical diagnosis of toxic adenoma of the thyroid was made and the growth was surgically removed. Histological examination showed a colloid adenoma.

The patient's convalescence was uneventful and he was discharged on the ninth postoperative day. He remained well until September 1, 1939 when he developed gonorrhea. He visited his physician who prescribed sulfanilamide, 30 grains daily, and told him to return in three days. The patient returned complaining that the medicine had made him nauseated. The prescription was changed to 30 grains of Neo-Prontosil daily and he was told to return in three days. He did not return but continued to take the drug in the amount prescribed. During a period of six weeks he consumed 1,250 grains. He then developed malaise and weakness and discontinued the drug. Ten days later he again consulted his physician who noted slight jaundice and ordered a high carbohydrate diet and told him to return the next day. One week later he returned to his physician who noted an increase in the jaundice and the patient was admitted to the hospital for observation. Four hours after admission he became delirious and lapsed into a coma from which he did not recover. The jaundice rapidly increased in intensity; he developed auricular fibrillation and died 36 hours after admission to the hospital.

Physical examination showed the area of liver dullness to be greatly reduced. Over the trunk and extremities were numerous petechial hemorrhages. Blood chemical studies showed: sugar 58.0 mg. per cent; N.P.N. 32.4 mg. per cent; creatinine 1.41 mg. per cent; icterus index 182.8.

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From the Department of Pathology, St. Agnes Hospital.

Since the normal liver can excrete more bilirubin than is brought to it, according to Rich,<sup>14</sup> blood destruction per se, with its uncomplicated excess production of bilirubin, is very seldom a cause of jaundice except in rare instances when the hemolytic process is of extreme degree. Excess production of bilirubin, however, is practically always associated with other conditions which tend to impair the excretory power of the liver. Up to a certain point the reserve power of the liver can take care of the excess bilirubin to prevent jaundice. No form of jaundice results purely from a functional depression of the excretory power of the liver, i.e., without actual loss of cells through necrosis. If jaundice does occur from excess bilirubin production, it results from the combination of increased demand upon the liver and decreased excretory power.<sup>14</sup>

Overproduction of bilirubin is ordinarily associated with conditions other than mere overstrain which tend to depress the excretory power of the liver, e.g., anoxemia, etc. It is known that in experimental anoxemia, necrosis of liver cells occurs without a resulting jaundice. If hemoglobin or bilirubin is injected in addition, however, jaundice develops at once.<sup>13</sup> Necrosis or cellular damage reduces the amount of functioning liver tissue and impairs its excretory function. If excess bilirubin is produced, such a liver will be unable to excrete it all and jaundice will result from the retention of excess pigments. It is thus evident that in hemolytic anemias both factors (depressed excretory function due to anoxia and increased production of bilirubin) are present just as in the experimental animal.

When jaundice is noted following drug administration, one must postulate that liver damage or toxic hepatitis is present. Furthermore, Weir<sup>15</sup> has pointed out that hepatitis, even to the extent of fatal acute yellow atrophy, can occur without jaundice. In the 408 cases (101 children and 307 adults) Long et al.<sup>5</sup> studied they found the incidence of jaundice without anemia to be 0.6 per cent, all in adults. If subsequently a hemolytic process supervenes, the drug has extended its activity to the hematopoietic system and the jaundice should deepen because of the increased bilirubin production.

The reason the above facts are being emphasized in this presentation is that in the cases previously reported the presence of jaundice in hemolytic anemias has been ascribed mainly to the hemolytic process and the factor of liver damage has been minimized or overlooked.

The mechanism of injury to the kidney has not been elucidated and the effect on kidney function not determined, and they merit investigation. In this connection it is interesting to note that experimental observation<sup>16</sup> reveals no impairment of renal function by sulfanilamide in therapeutic doses. Ottenberg<sup>9</sup> also experienced some difficulty in attributing the renal damage in his case solely to the sulfanilamide since his patient was receiving milk injections concomitantly. Cases presenting nephritis alone as a toxic manifestation of sulfanilamide would help to settle this problem.

### CONCLUSION

Two cases of toxic hepatitis, acute hemolytic anemia, and renal damage following sulfanilamide therapy have been presented and discussed. Attention has been called to the presence of liver damage in all cases where jaundice is evident.

## DISCUSSION

The mode of action of the drug in producing fatal necrosis of the liver is not known. This case serves to further emphasize the importance of close observations on every patient receiving sulfanilamide or any closely allied drugs. This patient complained of nausea following the initial doses of the drug. It would seem advisable to discontinue this type of therapy at the onset of any toxic manifestation, especially in the treatment of such a disease as gonorrhea where the mortality rate is low and other methods of treatment are effective.

It has long been known that massive hemolysis from transfusion of incompatible blood, blackwater fever, etc., results in hemoglobinuria and oliguria and sometimes terminates fatally in uremia. DeGowin, Warner and Randall<sup>8</sup> have reviewed earlier work on the pathogenesis of the renal insufficiency complicating massive hemolysis and have published original studies from which they concluded that the nitrogen retention is due to two factors: (1) tubular obstruction from precipitation of hemoglobin in the loops of Henle; (2) tubular degeneration and necrosis with edema of the interstitial tissue. Finding further that hemoglobin transfused into dogs readily precipitated in the renal tubules if the urine was acid, but remained in solution if the urine was alkaline, they advised prompt alkalization whenever hemoglobinuria was anticipated or encountered.

To draw attention to the occasional association of massive hemoglobinuria and uremia with sulfanilamide hemolytic anemia, the following case is reported.

#### CASE REPORT

M. M., a 38-year-old colored male, was admitted to Detroit Receiving Hospital on April 10, 1939, complaining of chills, fever and pain in the chest. For three weeks prior to admission, he had a cough productive of yellowish sputum. On the day of admission he suddenly developed a sharp shooting pain in the right lower chest. Shortly after this he had a severe chill, followed by fever and rusty sputum. Past history was not significant except for pneumonia in 1923. Physical examination revealed a well-developed, well-nourished colored male, moderately dyspneic, and acutely ill. Temperature was 101.6° F., pulse 118, respirations 30. Blood pressure 100 mm. of mercury systolic, 70 mm. diastolic. There was evidence of early consolidation of the right middle and right lower lobes. This was confirmed by roentgen examination. The remainder of the physical examination was negative.

*Laboratory:* Urine: Specific gravity 1.024; trace of albumin; occasional casts. Blood: Hemoglobin 11 grams; red blood cells 4,330,000; white blood cells 33,000; polymorphonuclear neutrophils 94 per cent, filamented 18, non-filamented 76 per cent; lymphocytes 6 per cent. Kline test negative. Neufeld examination of sputum revealed type VIII pneumococcus. Blood culture taken on admission was positive for type VIII pneumococcus.

*Acute Hemolytic Anemia with Hemoglobinuria.* Between 11:00 p.m. on April 10, and 8:00 p.m. on April 13, the patient received a total of 460 grains of sulfanilamide and 415 grains of sodium bicarbonate. On the morning of the twelfth, the blood culture was negative and the temperature, pulse and respirations reached normal. The patient was listless, drowsy and cyanotic at this time but showed no jaundice nor fall in hemoglobin. During the evening of April 12, the temperature rose to 102°, and the next day the urine became dark red in color. Only an occasional red blood cell was discovered on microscopic examination of the urine, whereas large amounts of hemoglobin were found on spectroscopic and chemical analysis. Sulfanilamide was discontinued, whereas sodium bicarbonate was increased to 180 grains and then to 240 grains daily in an attempt to render the urine alkaline. On April 13, the hemoglobin concentration in the blood was 10.0 gm. per 100 c.c. which represented a drop of 1.0 gm. per cent from the admission level. By the following day, the hemoglobin had fallen to 7.0 gm., the red blood count to 1,980,000, and the icterus index had risen to 50. The hemoglobinuria persisted for 24 hours longer, during which time the anemia increased in spite of a transfusion, the red blood count reaching a minimum of 1,650,000 with 5.0 gm. hemoglobin per 100 c.c. on April 15. Methemoglobinemia was detected spectroscopically on April 14 and 15, but disappeared on April 16. The blood fragility to hypotonic saline was normal.

ilar reagin-like factor (Dreyer and Walker,<sup>2</sup> Browning,<sup>3</sup> Meinicke<sup>4</sup> and Vernes<sup>5</sup>). Malloy and Kahn,<sup>6</sup> and Barnett, Jones and Kulchar<sup>7</sup> have experimentally demonstrated such a substance in normal serum, but in quantities less than those required to give positive or even doubtful diagnostic tests. Eagle<sup>8</sup> conducted a study of the serologic tests for syphilis on a group of 40,545 white college students. The number of presumably normal persons giving positive tests in the absence of clinical evidence or history of syphilitic infection was small, 1 in 1125 persons tested, and internal evidence suggested that some of these actually had latent syphilis. Nevertheless it seems possible that the serum of an occasional normal person may contain the reagin-like factor in sufficient concentration to give a biologic false positive serologic test for syphilis. It is important that this possibility be kept in mind, particularly in those states in which premarital and prenatal serologic tests are compulsory.

The third and last group of false positive serologic tests are those associated with some organic disease other than syphilis, generally an acute infection. The occurrence of these false positive tests in yaws, leprosy, malaria and infectious mononucleosis has been thoroughly established. Other diseases which have been reported to give false positive tests are: relapsing fever, rat-bite fever, scarlet fever, tuberculosis, pneumonia, Vincent's infection, malignancy (particularly carcinoma of the tongue), subacute bacterial endocarditis, glanders, Weil's disease, leishmaniasis, lymphopathia venereum, chancroid, trypanosomiasis, typhus fever, vaccinia, upper respiratory infections, rheumatic fever, and injections of horse serum. There are also reports to the effect that certain chemicals, when present in the blood stream, will produce false positive tests; ether anesthesia has been incriminated many times in the older literature; acetic acid poisoning and sulfanilamide have recently been suggested as causing false positive tests.

There is no doubt that some and perhaps many of these diseases will actually cause biologic false positive serologic tests for syphilis. A systematic study with respect to the frequency with which false positive tests do occur is urgently needed. It was not until Ester<sup>9</sup> and Kitchen, Webb and Kupper<sup>10</sup> inoculated nonsyphilitic persons with malaria and tested

<sup>2</sup> DREYER, G., and WALKER, E. W. A.: Neues zur Theorie der Wassermannschen Reaktion, *Biochem. Ztschr.*, 1913, liv, 11.

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<sup>4</sup> MEINICKE, E.: Theorie und Methodik der serologischen Luesdiagnostik, *Deutsch. med. Wchnschr.*, 1919, xlv, 178.

<sup>5</sup> VERNES, A.: Sur la précipitation d'un colloïde organique par le serum human normal ou syphilitique, *Compt. rend. Acad. d. sci.*, 1918, clxvi, 575.

<sup>6</sup> MALLOY, A. M., and KAHN, R. L.: The ultramicroscopic precipitation reaction in syphilis, *Jr. Infect. Dis.*, 1931, xlviii, 243.

<sup>7</sup> BARNETT, C. W., JONES, R. B., and KULCHAR, G. V.: Measurement of reagin in non-syphilitic sera, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxiii, 214.

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<sup>9</sup> ESTER, F.: Sul comportamento di alcune sieroreazioni della sifilide sul siero di sangue dei non luetici inoculati sperimentalmente con malaria terzana benigna, *Gior. di batteriol. e immunol.*, 1936, xvii, 502.

<sup>10</sup> KITCHEN, S. F., WEBB, E. L., and KUPPER, W. H.: The influence of malarial infection on the Wassermann and Kahn reactions, *Jr. Am. Med. Assoc.*, 1939, cxii, 1443.

*Oliguria, Nitrogen Retention.* The urinary output was surprisingly good for about 60 hours after the onset of the hemoglobinuria. On April 16, however, the 24 hour output fell to 700 c.c. and on April 17, to 525 c.c. The maximum specific gravity during these two days was 1.015. In the meantime, the physical signs of consolidation disappeared, partial resolution of the pneumonic process being noted in a roentgenogram taken on April 17. From April 18 to April 20, the average daily intake was 5,000 c.c., the average urinary output was below 1,000 c.c. During this period the blood urea remained in the vicinity of 150 mg. per cent. On April 21, the output jumped to 2,200 c.c. and thereafter it ranged between 2,500 and 3,000 c.c. daily. The blood urea gradually fell, reaching 34 mg. per cent on April 28 and remaining normal thereafter. The urinary specific gravity remained low until just before discharge, when it reached 1.020.

*Anasarca.* Since sodium bicarbonate in a dose of 240 grains daily, together with an alkaline ash diet did not render the urine alkaline, the daily dose was increased to 480 grains on April 19. Three days later, the urine became alkaline and remained so during the administration of soda. On April 19, a small right pleural effusion was found and puffiness of the face was noted. By April 24, the entire right half of the chest was flat to percussion and opaque on roentgen examination. During the next week, 3,650 c.c. of clear straw colored fluid were removed. Although the specific gravity was 1.020 and the albumin content was 26 gm. per liter, the fluid was not inflammatory, as shown by a cell count of 42 lymphocytes and 11 polymorphonuclears per cu. mm. The subcutaneous edema steadily increased, and by April 26, a marked generalized anasarca and moderate ascites were present. Blood pressure at this time was 154 systolic and 90 diastolic. Serum albumin was 3.2 gm. per 100 c.c.; serum globulin 2.1 gm. per 100 c.c. Between April 26 and May 4, the edema steadily diminished in spite of an average daily intake of 200 grains of sodium bicarbonate. Theobromine sodium salicylate was administered in a dose of 60 grains daily during this period but there was no clear cut evidence that it was responsible for the reduction in edema. By May 4, the serum albumin had risen to 4.2 gm. per cent, the globulin to 2.37 gm. per cent.

*Result.* At discharge, the edema and ascites had disappeared, the lungs were clear, the blood pressure was normal, the urine was negative and the red blood count and hemoglobin were above the admission level. Physical examination on October 17, 1939 revealed no abnormalities. The red blood count was 5,150,000, the hemoglobin 14.5 gm. per 100 c.c. The urine was entirely negative. On urea clearance test, 90.6 c.c. of blood were cleared per minute with a urinary volume of 2.5 c.c. per minute.

### SUMMARY

Acute hemolytic anemia with hemoglobinuria, uremia and anasarca developed in a patient who had taken 460 grains of sulfanilamide over a period of 60 hours for the treatment of type VIII pneumococcic pneumonia. A complete recovery was made.

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2. LONG, P. H., BLISS, E. A., and FEINSTONE, W. H.: Mode of action, clinical use and toxic action of sulfanilamide, Jr. Am. Med. Assoc., 1939, cxii, 115.
3. WOOD, W. B., JR.: Jr. Am. Med. Assoc., 1938, cxi, 1916.
4. BOHLMAN, H. R.: Use of sulfanilamide, Dis. of Chest, 1937, iii, 24.
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## REVIEWS

*The Patient as a Person.* By G. CANBY ROBINSON. 423 pages; 16 × 23.5 cm. The Commonwealth Fund, 41 East 57th St., New York, N. Y. 1939. Price, \$3.00.

The author, well known for his career in medical education and in medical investigation, has gone back to fundamentals in medical care through a study of the factors in the illness of 174 unselected patients admitted to the Johns Hopkins Hospital. Illness he defines as "a state in which some of the natural functions of the body are disturbed so that the patient cannot meet the usual requirements of life without pain or discomfort. . . ." In the production of illness it is evident that organic disease is only one factor and that emotional disturbances resulting from various strains and dissatisfactions are often superadded to disease as an element in the illness or in themselves may induce illness.

The patients studied are grouped according to their presenting symptoms, circulatory symptoms, respiratory symptoms, infections, diabetic, etc. They were studied not only as patients in the clinic but as individuals in their home setting.

It will not surprise physicians whose lives have been spent in private practice that the author finds that the outpatient department does not give adequate attention to the rôle of the emotional disturbances in the illness of its patients and that moreover there are serious difficulties in the way of improving this state of affairs. Certain helpful suggestions are offered for the inclusion in outpatient routine of personal conferences of the physician and patient on the background of the latter's illness.

The fundamental difficulty which is not referred to would seem to be that the division of medical care into home care, outpatient care (or office care) and hospital care places the patient under too many different physicians and tends to restrict the interest of the hospital and outpatient physicians to the simpler and more objective factors in the patient's illness to the exclusion of the no less important factors of environment and social relations, which are often quite obvious to the physician who visits the home. The well trained general practitioner who has access to the hospital's diagnostic and therapeutic facilities and to its consultant services is in the best position to assess accurately the nature of the patient's illness and the wisest program of therapy.

M. C. P.

*Bacterial Metabolism.* By MARJORY STEPHENSON, ScD., Associate of Newham College, Cambridge, Member of the Scientific Staff of the Medical Research Council. 391 pages; 14.5 × 22.5 cm. Longmans, Green and Company, Ltd., London, New York. 1939. Price, \$7.50.

This is an enlarged edition of a book which first appeared in the "Monographs of Biochemistry," Series 1930. Owing to the fact that our knowledge of bacterial biochemistry has rapidly increased it was necessary to reproduce it in a larger format.

Following the idea of the first edition it is an attempt to arrange the scattered data in this field in order to appraise our knowledge of the metabolic activities of bacteria. The chapters include respiration, the action of bacteria on polysaccharides and various proteins, protein decomposition products, nitrogen fixation, the metabolism of autotrophic microorganisms, and bacterial photosynthesis. The bibliography is especially complete. This volume is recommended to anyone who is interested in the biochemistry, and metabolism of bacteria.

J. G. Mc.A.

Examination of the blood showed no trace of sulfanilamide. A blood count showed: erythrocytes 5,700,000; leukocytes 13,450; hemoglobin 16.3 gm., 96 per cent (Newcomer).

A differential count of the leukocytes showed in each 100 white blood cells: metamyelocytes II 18; mature neutrophils 68; lymphocytes 6; monocytes 8.

*Summary of Autopsy Findings.* Postmortem examination performed by the author revealed a well-developed and well-nourished white male body obviously intensely jaundiced. There were numerous petechial hemorrhages in the skin over the trunk and lower extremities. The pertinent findings on examination of the organs were petechial hemorrhages involving all the serosal surfaces including visceral and

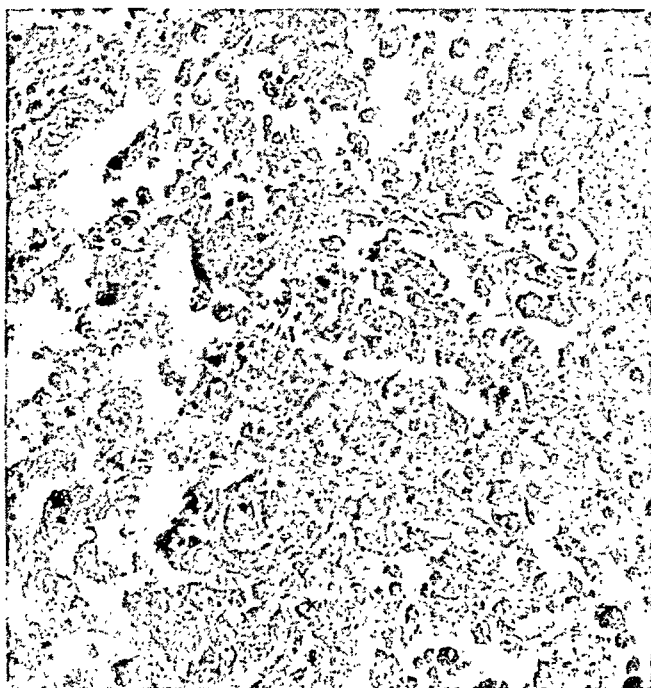


FIG. 1. Section showing necrosis of liver cells. Hematoxylin eosin.  $\times 480$ .

parietal pleura, pericardium and peritoneum. There was rather extensive subarachnoid hemorrhage involving both parietal areas. The most important finding was marked reduction in size of the liver. It weighed 600 grams. The capsular surface was wrinkled and the organ was flabby in consistence. On section the liver parenchyma presented a mottled appearance with red, yellowish and grayish areas being irregularly distributed. These changes completely obliterated the usual liver pattern. The gall bladder contained thin colorless mucus. The kidneys showed marked cloudy swelling.

Histological examination of the liver showed advanced necrosis of the liver cells. The nuclei had lost the power of staining with basic dyes; the cytoplasm had disintegrated leaving the outline of the cells indefinite. In many areas irregular granular masses and cellular debris were all that remained of the liver cells. The connective tissue structure and masses of necrotic cells were infiltrated by lymphocytes. Sections from many different areas of the liver showed similar lesions.



# COLLEGE NEWS NOTES

## GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged:

### Books

- Dr. Henry Joachim, F.A.C.P., Brooklyn, N. Y., 1940 Edition of "Practical Bedside Diagnosis and Treatment";  
Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn., autographed copy of "Clinical Diabetes Mellitus and Hyperinsulinism."

Acknowledgment is also made of the receipt of a bound book entitled "Graduate Medical Education," which is a report of the Commission on Graduate Medical Education. Dr. Willard C. Rappleye, F.A.C.P., Dean of Columbia University College of Physicians and Surgeons, is Chairman of the Commission. Other members of the Commission include Dr. James D. Bruce, F.A.C.P., President of the American College of Physicians and Vice President of the University of Michigan; Dr. Anton J. Carlson, F.A.C.P., Hixon Distinguished Service Professor of Physiology of the University of Chicago; Dr. Walter F. Donaldson, F.A.C.P., Secretary of the Medical Society of the State of Pennsylvania; Dr. Reginald Fitz, F.A.C.P., Regent of the American College of Physicians, Assistant to the Dean and Lecturer on the History of Medicine, Harvard University Medical School; and Dr. John B. Youmans, F.A.C.P., Associate Professor of Medicine and Director of Postgraduate Instruction at Vanderbilt University.

### REPRINTS

- Dr. Sidney Adler (Associate), Detroit, Mich.—1 reprint;  
Dr. Thomas W. Baker, F.A.C.P., Charlotte, N. C.—1 reprint;  
Dr. Miles J. Breuer, F.A.C.P., Lincoln, Nebr.—1 reprint;  
Dr. Clyde Brooks, F.A.C.P., New Orleans, La.—3 reprints;  
Dr. A. David Cloyd (Associate), Omaha, Nebr.—1 reprint;  
Dr. George H. Coleman, F.A.C.P., Chicago, Ill.—1 reprint;  
Dr. Erle B. Craven, Jr., F.A.C.P., Lexington, N. C.—2 reprints;  
Dr. Bruce H. Douglas, F.A.C.P., Detroit, Mich.—3 reprints;  
Dr. H. R. Edwards, F.A.C.P., New York—3 reprints;  
Dr. Edward Gipstein (Associate), New London, Conn.—1 reprint;  
Dr. Augustus A. Hall, F.A.C.P., Columbus, Ohio—1 reprint;  
Dr. B. R. Heninger, F.A.C.P., New Orleans, La.—1 reprint;  
Dr. Leslie R. Kober (Associate), Phoenix, Ariz.—2 reprints;  
Dr. Victor W. Logan (Associate), New York—2 reprints;  
Dr. John I. Marker, F.A.C.P., Davenport, Iowa—1 reprint;  
Major Horace P. Marvin, F.A.C.P., (MC), U. S. Army—1 reprint;  
Dr. Thomas H. McGavack, F.A.C.P., New York—6 reprints;  
Dr. Robert C. Page (Associate), Mount Vernon, N. Y.—3 reprints;  
Dr. H. Malcolm Read (Associate), York, Pa.—1 reprint;  
Dr. Howard A. Rusk, F.A.C.P., St. Louis, Mo.—4 reprints;  
Dr. Frederick R. Taylor, F.A.C.P., High Point, N. C.—1 reprint;  
Dr. Jefferson J. Vorzimer (Associate), New York—1 reprint;  
Dr. R. Lomax Wells, F.A.C.P., Washington, D. C.—1 reprint;  
Dr. Howard F. West, F.A.C.P., Los Angeles—3 reprints.

## EDITORIAL

### *BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS FOR SYPHILIS*

SINCE the introduction of the Wassermann test in 1906, opinion as to the specificity of serologic tests for syphilis, if reports in the literature reflect the general impressions of the times, has passed through three distinct phases. From 1906 to 1918, many organic diseases, as well as pregnancy, menstruation, and the effect of various drugs, were reported to cause false positive Wassermann tests. In the period 1918 to 1928, these false positive tests were thought to be due to faulty technic or the associated presence of symptomless syphilis, and serologic tests for syphilis were regarded as amazingly specific.

From 1928 to the present, the pendulum is again swinging back. It now becomes clear that many "false positive" tests are due not to technical but to biologic factors.

Two developments have contributed to this reversal of opinion. One is the great increase in the number of serologic tests performed. Because of laws in many states compelling premarital and prenatal serologic tests for syphilis, and their greatly increased routine use in medical practice, many normal persons or those suffering from infections other than syphilis have been found to give biologic false positive tests.

A second and more important factor is the increased sensitivity of modern serologic tests for syphilis. In 1918 Meinicke devised a workable flocculation test which was later improved by Kahn; these original tests of Meinicke and Kahn were less sensitive by 10 to 15 per cent than tests developed after 1928. Hand-in-hand with increased sensitivity came the tendency of these tests to give occasional false positive reactions.

In general, false positive reactions may be of three types. Most frequent are technical false positive reactions due to laboratory errors, which may occur with any type of test. These technical errors are readily recognizable, should cause no confusion in diagnosis and need not be further considered here.

A second category is the biologic false positive tests occasionally encountered in normal persons who have neither syphilis nor any other organic disease. The presence of a reagin-like substance has repeatedly been demonstrated in the serum of many normal animal species other than man. The literature on this subject has recently been exhaustively reviewed by Kemp.<sup>1</sup> The serum of normal human beings has also been thought to contain a sim-

<sup>1</sup> KEMP, J. E., FITZGERALD, E. M., and SHEPHERD, M.: The occurrence of positive serologic tests for syphilis in animals other than man, with a review of the literature, *Am. Jr. Syph., Gonor. and Ven. Dis.* (In Press.)

injections, under Dr. Torald Sollmann, F.A.C.P., and Dr. Joseph Seifter of the Department of Pharmacology.

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Dr. Ramón M. Suárez, F.A.C.P., San Juan, College Governor for Puerto Rico, has been appointed Head of the Department of Clinical Medicine of the School of Tropical Medicine of the University of Puerto Rico, under the auspices of Columbia University.

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Dr. Edward J. Stieglitz, F.A.C.P., Garrett Park, Md., has been made Research Associate in Gerontology at the National Institute of Health. He will organize and develop a new unit of research, to deal with the many problems of aging.

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Dr. Ralph Pemberton, F.A.C.P., Philadelphia, was recently elected an Honorary Fellow of the Royal Society of Medicine of London, England.

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Dr. Lowell S. Selling, F.A.C.P., Detroit, addressed the New York meeting of the American Medical Association, June 14, on "The Mental Hygiene Aspect of the Traffic Accident."

Dr. Selling also addressed the American Psychiatric Association at Cincinnati, May 24, on "The Psychopathology of the Hit-and-Run Driver." He was elected Chairman of the Section on Forensic Psychiatry and has also been elected to the office of Second Vice President of the American Psychopathological Association and a member of the Advisory Editorial Boards of the "Journal of Criminal Law and Criminology" and the "Journal of Criminal Psychopathology."

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Dr. Cecil M. Jack, F.A.C.P., Decatur, Ill., has been made an honorary member of the Macon County Tuberculosis and Visiting Nurse Association by the Organization's executive committee.

Dr. D. O. N. Lindberg, F.A.C.P., is Medical Director and Superintendent of the Macon County Tuberculosis Sanatorium.

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The Omaha Mid-West Clinical Society will hold its eighth annual assembly October 28–November 1, 1940. Among the guests who will present addresses and clinics are Dr. Samuel Ayres, Jr., F.A.C.P., Los Angeles (Dermatology); Dr. Frank H. Bethell, F.A.C.P., Ann Arbor, Dr. Reginald Fitz, F.A.C.P., Boston, Dr. Frank J. Heck, F.A.C.P., Rochester, Minn., and Dr. George R. Herrmann, F.A.C.P., Galveston (Medicine); Dr. Wendell S. Muncie (Associate), Baltimore (Neurology); Dr. Horton R. Casparis, F.A.C.P., Nashville (Pediatrics); and Dr. John T. Murphy, F.A.C.P., Toledo (Radiology).

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Dr. Henry T. Smith, F.A.C.P., McGehee, was installed as President of the Arkansas Medical Society at its recent session in Fort Smith.

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Dr. Lewis B. Flinn, F.A.C.P., Wilmington, President of the Delaware Academy of Medicine, was toastmaster at a banquet on May 9 to observe the tenth anniversary of the founding of the Academy. Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, was the guest speaker.

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Dr. Paul D. White, F.A.C.P., Boston, addressed the Washington (D. C.) Academy of Medicine May 16 on "The Heart in Middle Life."

specimens of blood taken daily from the time of inoculation to several weeks after the temperature became normal that it was realized that not 10 to 15 per cent, as was formerly believed, but a large proportion of the sera (in their series, 90 to 100 per cent) of persons infected with tertian malaria gave biologic false positive tests for syphilis at some time during the course of the infection. A similar approach applied to all the diseases listed above would certainly provide data of clinical significance.

Clarification of the incidence of false positive serologic tests for syphilis in other diseases depends on recognition of the possible transitory nature of biologic false positive tests, and the necessity of repeated tests during the entire course of the disease, continuing well into the convalescent period or until the false reactions have permanently reversed to negative. The application of a quantitative serologic technic to those sera found to be positive should provide data of interest and possible value in the differentiation of biologic false positive tests from those due to actual syphilitic infection.

The complicated nature of the clinical and serologic procedures essential to differentiate biologic false positive tests from those due to syphilitic infection has recently been briefly outlined by Moore<sup>11</sup>; and a new test for this particular purpose (the so-called "verification" test) has just been described by Kahn.<sup>12</sup>

C. F. M.

<sup>11</sup> MOORE, J. E.: A suggested method of approach to the recognition of the biologic false positive serologic test for syphilis, *Bull. Genitoinfect. Dis.*, 1940, iii, 1.

<sup>12</sup> KAHN, R. L.: A serologic verification test in the diagnosis of latent syphilis, *Arch. Dermat. and Syph.*, 1940, xli, 817.

Dr. Buford H. Wardrip (Associate), San Jose, Calif., is President of the newly organized California Trudeau Society.

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Dr. William D. Stroud, F.A.C.P., Philadelphia, was one of the guest instructors on the eighth annual postgraduate course of Indiana University School of Medicine, Indianapolis, May 6-11.

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Dr. Edward C. Humphrey (Associate), Somerset, Ky., recently resigned as Health Officer of Pulaski County to accept a like position in Mercer County.

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Dr. Priscilla White, F.A.C.P., and Dr. Alexander Marble, F.A.C.P., both of Boston, were guest speakers before the Medical Society of the County of Kings, New York, May 21, their subjects being "Diabetes in General and in Relation to Pregnancy" and "Diabetes in Relation to Surgery," respectively.

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Dr. Oscar Costa-Mandry, F.A.C.P., San Juan, addressed the Humacao (P. R.) District Medical Society May 5 on "Extension of Laboratory Service in Puerto Rico."

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Dr. Rafael Rodriguez Molina, F.A.C.P., San Juan, recently gave an address on "Sprue in the Puerto Rican Indigent" before the School of Tropical Medicine of the University of Puerto Rico.

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Dr. Robert B. Hiden (Associate) has been made senior assistant medical director of the Austen Riggs Foundation, Inc., at Stockbridge, Mass.

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Dr. Clarence A. Smith, F.A.C.P., Seattle, addressed the Medical Library Association at Portland, Ore., during its forty-second annual meeting, June 25-27, on "Growth, Development and Problems of a Regional Medical Periodical."

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The National Research Council, through its division of medical sciences, recently appointed committees to coöperate with the Medical Corps of the U. S. Army and Navy. Among appointees are the following: Dr. Francis G. Blake, F.A.C.P., New Haven, Committee on Chemotherapeutic and Other Agents and Chairman of the Subcommittee on Infectious Diseases; Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Committee on Transfusions.

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The Vancouver Medical Association conducted an "annual summer school" at Vancouver June 25-28. Dr. William S. Middleton, F.A.C.P., Madison, Wis., was one of the lecturers.

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Dr. George W. McCoy, F.A.C.P., for more than 40 years in the active service of the U. S. Public Health Service, retired on June 30. Dr. McCoy had been Medical Director of Studies on Prevalence and Spread of Leprosy in the U. S. Public Health Service, Professor of Preventive Medicine and Public Health at Louisiana State University Medical Center, New Orleans, Examiner and Member of Basic Science Board and National Board of Medical Examiners, a member of the Council on Pharmacy and Chemistry of the American Medical Association and a member of the U. S. Pharmacopoeia Revision Committee.

*Leukemia and Allied Disorders.* By CLAUDE E. FORKNER, M.D. 333 pages; 16 × 24 cm. Macmillan Company, New York. 1938. Price, \$5.00.

The author has provided an excellent monograph for the use of the internist. The section on pathologic physiology will be particularly stimulating since much of the information it contains has not heretofore been readily accessible. Likewise there is gathered together under the heading of "Systematic Survey of the Organs and Organ Systems" a very readable account of the ways, both common and rare, in which leukemia may involve all parts of the body. The literature is very fully presented so that more detailed reports on an individual complication become readily accessible.

Later the clinical aspects of the various forms of leukemia are very adequately covered and the leukemoid states described.

The author's attitude in therapy is conservative but most recent and old measures are evaluated. The volume is one which will often be profitably referred to by all students of internal medicine.

M. C. P.

*Pneumonia and Its Nursing Care.* By HERBERT K. ENSWORTH, B.S., M.D., and LELA GREENWOOD, R.N.; with a foreword by RUSSELL L. CECIL, M.D. 177 pages; 11 × 17.5 cm. J. B. Lippincott Co., Philadelphia. Price, \$1.50.

This book, written for nurses, deals briefly with the problem of pneumonia. All points are adequately covered including etiology, pathology, symptoms, various methods of therapy, and nursing care. The authors unfortunately have failed to mention the subcutaneous method of administering sulfapyridine, though the unaccepted new drugs, sulfathiazole and sulfamethylthiazole, have been mentioned. The bibliography divided for each chapter at the end of the book has been well selected. The subject matter is clear-cut and well presented.

This book will prove most useful to graduate nurses who see only an occasional pneumonia case and want a quick review of the subject. Likewise, public health nurses because of their increased responsibility to the indigent pneumonia case, especially in those states with pneumonia control campaigns, will find this small volume helpful.

K. W.

*OBITUARIES*

## DR. DAVID RIESMAN

Dr. David Riesman, aged 73 years, died in the University of Pennsylvania Hospital Monday, June 3, 1940. Members of his immediate family were with him at the end. In his passing, American medicine has lost one of its most distinguished leaders. Dr. Riesman had been ill for several months. An autopsy revealed a small carcinomatous growth in the lower bowel with generalized metastasis.

Dr. Riesman was born March 25, 1867, near Eisenach in Saxe-Weimar, Germany. In his boyhood, he was brought to Portsmouth, Ohio, where he was graduated from the public high school. He entered the University of Michigan in 1889, but after a course of one year he came to the University of Pennsylvania School of Medicine in 1890 and graduated in 1892, following which he became an instructor of pathology at the University and began his internship at Philadelphia General Hospital, where he continued to serve throughout his lifetime as pathologist, visiting physician and president of the medical board.

In 1900 he became instructor of clinical medicine in the University and in 1912 succeeded the late Dr. John H. Musser to the professorship until 1933, when he retired from routine teaching. At the time he was stricken, his weekly routine included two lectures at the University, consultations at seven hospitals along with the conduction of an ever-growing practice.

Dr. Riesman was consultant to the University of Pennsylvania Hospital, Philadelphia General, Women's College, Jewish, Chestnut Hill, Kensington and Graduate Hospitals. During a visiting lecture series at Harvard University in 1927, he was physician-in-chief of Brigham Hospital, Boston.

A host of societies claimed his active membership. Among those of which he had been president are: Philadelphia County Medical Society, Philadelphia Pathological Society, American Society of Medical History, Northern Medical Association, Interstate Postgraduate Medical Assembly of North America, Inter-Urban Clinical Club, Philadelphia Heart Association, and the American Gastro-enterologic Association.

Dr. Riesman was also a member of the Philadelphia College of Physicians, Medical Society of the State of Pennsylvania (formerly chairman of the Section on the Practice of Medicine), American Medical Association, American Association for the Advancement of Science, Medieval Academy of America, French Prehistoric Society, British Philosophical Association, American Board of Internal Medicine (Adviser and Diplomate), American College of Physicians (Fellow since January 1, 1921), History of Science Society, Foreign Policy Association, University Club, Franklin Inn Club and numerous other Philadelphia Societies, including Neurological, and Pediatric societies.

The ninety-first annual session of the American Medical Association was held in New York City June 10-14. Dr. Nathan B. Van Etten, F.A.C.P., New York, was inducted as President and Dr. Frank H. Lahey, Boston, was made President-Elect. Aside from the scientific program, action that drew most attention was the creation of a Committee on Preparedness to "establish and maintain contact and suitable relationship with all governmental agencies concerned with the prevention of disease and the care of the sick . . . to make available . . . every facility . . . for the health and safety of the American people and the maintenance of American democracy." The House of Delegates unanimously adopted a report embodying two resolutions, one in the form of a plan for military medical care proposed by the Surgeon General of the U. S. Army, and the other offering the services of the American Medical Association in a national emergency. The specific resolutions follow:

RESOLVED, that the House of Delegates authorize the Board of Trustees to create a Committee on Medical Preparedness, to consist of seven members of this House, with the President of the Association, the Secretary of the Association, the Secretary of the Board of Trustees and the Editor as ex officio members; and be it further

RESOLVED, that this Committee establish and maintain contact and suitable relationship with all governmental agencies concerned with the prevention of disease and care of the sick, in both civil and military aspects, so as to make available at the earliest possible moment every facility that the American Medical Association can offer for the health and safety of the American people and the maintenance of American democracy.

The Committee appointed, to be under the Chairmanship of Dr. Irvin Abell of Louisville, includes Drs. James E. Paullin, F.A.C.P., Atlanta; Stanley H. Osborn, Hartford; Walter G. Phippen, Boston; Harvey B. Stone, Baltimore; Fred W. Rankin, Lexington; Roy W. Fouts, Omaha; Samuel E. Thompson, F.A.C.P., Kerrville, Tex.; Charles A. Dukes, Oakland; and John H. O'Shea, Seattle. Ex officio members are Drs. Nathan B. Van Etten, F.A.C.P., Olin West, Arthur W. Booth, Austin B. Hayden and Morris Fishbein.

The New York session, the first since 1917 in New York City, is said to have had a registration of over twelve thousand, the largest on record.

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At the recent annual meeting of the American Gastro-enterological Association, Atlantic City was selected for the next meeting, May 5-6, 1941. The following officers were elected for the coming year: Dr. Andrew C. Ivy, F.A.C.P., Chicago, President; Dr. Russell S. Boles, F.A.C.P., Philadelphia, First Vice President; Dr. Sara M. Jordan, F.A.C.P., Boston, Second Vice President; Dr. Thomas T. Mackie, F.A.C.P., New York, Secretary; Dr. A. H. Aaron, F.A.C.P., Buffalo, Treasurer; and Dr. J. Arnold Barger, F.A.C.P., Rochester, Minn., Recorder. Dr. Ernest H. Gaither, F.A.C.P., Baltimore, was elected a member of the Council.

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Dr. Laurrie D. Sargent, F.A.C.P., Washington, Pa., as Trustee and Councilor of the Eleventh Councilor District of the Medical Society of the State of Pennsylvania, presided over a meeting of the District at Johnstown, Pa., June 20, 1940. Dr. Belford C. Blaine (Associate), Pottsville, Pa., Chairman of the State Society's Commission on Diabetes, gave a report on the control of diabetes in the State. Reports were received on County Society activities in the District, as well as reports on industrial health and other timely topics.

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Western Reserve University recently announced that the John and Mary R. Markle Foundation of New York has made a grant of \$2,000 to Western Reserve University School of Medicine to support an investigation of intravenous bismuth



staff and consultant of the Toronto General Hospital and Hospital for Sick Children. He won many honors during his distinguished military career and served continuously during the last war with the Canadian Army Medical Corps. He had been with the corps since its inception in 1900.

Born at Kirkton, Perth County, Dr. Fotheringham was the son of the late Rev. John and Helen Telfer Fotheringham. He received his early education at St. Mary's Collegiate Institute. Graduating in 1883 from University College, Toronto, with first-class honors in classics, he devoted several years to teaching and at one time was classics master at Upper Canada College. He graduated from Trinity Medical College in 1891 as a silver medalist and at the same time received the degree of M.B. from the University of Toronto.

Enlisting with "K" Company, Queen's Own Rifles, in 1879, he was appointed surgeon-lieutenant of the 12th Rangers in 1896. A year later he was transferred to the Queen's Own Rifles with the same rank.

At the outbreak of the last war in 1914 he enlisted for active service and was raised to the rank of colonel. He was appointed assistant director of medical services for Military District No. 2 and served overseas with the Second Canadian Division. In 1917 he was recalled from France to reorganize army medical services and was made director-general of military medical services for Canada, which office he held until 1920. On his return to Ottawa he was made a Major General.

He was awarded the C.M.G. while in France and was mentioned in dispatches several times. In 1924 he was gazetted honorary colonel of the Royal Canadian Army Medical Corps.

His academic career was equally brilliant and in 1892 he was appointed to the staff of Trinity Medical School as lecturer in therapeutics and clinical medicine. Following the amalgamation of Trinity Medical School with the University of Toronto he continued on the staff as assistant professor in clinical medicine. Dr. Fotheringham was the first incumbent of the chair established in 1924 by the University of Toronto in history of medicine. In 1918 he received the honorary degree of LL.D. from both the University of Toronto and from Queen's University. He was also created a Knight of Grace, the Order of St. John of Jerusalem. From 1919 to 1922 he was honorary surgeon to the Governor General of Canada at Ottawa.

As a physician he had served on the staff of St. Michael's Hospital, the Hospital for Sick Children and with the Toronto General Hospital. He was in charge of the outpatients' department, St. John's Hospital, from 1920 to 1930.

*Dr. Fotheringham was a life member and past president of the Canadian Military Institute, honorary life member and past president of the Academy of Medicine, member of St. Andrew's Society, the Corporation of Trinity College, the senate of the University of Toronto, Board of Management of Knox College, life member of the Canadian Medical Association and St. Andrew's Presbyterian Church. He was honorary consultant physician for*

Dr. Josiah J. Moore, F.A.C.P., Chicago, has been made President of the newly organized Illinois Society of Pathologists. Dr. Israel Davidsohn (Associate) of Chicago was made the Secretary-Treasurer.

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Among guest speakers at the annual meeting of the Iowa and Illinois Central District Medical Association at Davenport May 16 were: Dr. August A. Werner, F.A.C.P., St. Louis, "Anterior Pituitary Gonad Relationship in the Female"; Dr. Italo F. Volini, F.A.C.P., Chicago, "A Survey of Heart Disease"; and Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., "How Medicine Began."

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Dr. James H. Means, F.A.C.P. and Ex-President of the American College of Physicians, Boston, addressed the Academy of Medicine of Northern New Jersey May 14 on "Some Endocrinopathies for Which We Have Successful Specific Treatment."

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Among speakers before a symposium on arteriosclerosis at the Erdmann Auditorium, New York Post-Graduate Medical School and Hospital, June 6, were Dr. Nelson W. Barker, F.A.C.P., Rochester, Minn., "The Conservative Treatment of Arteriosclerosis Obliterans," and Dr. James G. Carr, F.A.C.P., Chicago, "Relation and Importance of Arteriosclerotic Disease in the Heart of Humans."

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Dr. Edgar A. Hines, F.A.C.P., Seneca, has been reelected Secretary for the thirty-first year of the South Carolina Medical Association.

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Dr. James G. Carr, F.A.C.P., Chicago, gave the presidential address before the Chicago Society of Internal Medicine May 27, his subject being "The Physician and the Internist."

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Announcement has been made that Dr. William deB. MacNider, F.A.C.P., Dean and Kenan Professor of Pharmacology at the University of North Carolina School of Medicine, Chapel Hill, will be awarded the George M. Kober Medal for 1941 for research on the liver and kidneys.

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The Montana State Medical Association held its annual meeting at Bozeman, June 19-20, under the Presidency of Dr. Harold W. Gregg, F.A.C.P., Butte.

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Dr. Wilburt C. Davison, F.A.C.P., Dean of Duke University School of Medicine, Durham, N. C., gave an address on "Opportunities in the Practice of Medicine" on the occasion of the dedication of new buildings for the Lynchburg (Va.) General Hospital, May 21.

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The Canadian Medical Association held its seventy-first annual meeting at Toronto, June 17-21, and was addressed, among others, by Dr. James H. Means, F.A.C.P., Boston, "The Diagnosis and Treatment of Hyperthyroidism," and Dr. Jonathan C. Meakins, F.A.C.P., Montreal, "Shock: Its Recognition and Treatment." Dr. Alan C. Brown, F.A.C.P., Professor of Pediatrics at the University of Toronto Faculty of Medicine, delivered the Blackader Lecture.

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Dr. Harry H. Wilson, F.A.C.P., Los Angeles, was installed as President of the California Medical Association at its recent annual meeting in Coronado.

## DR. JAMES WILSON HUNTER

Dr. James Wilson Hunter, F.A.C.P., of Norfolk, Virginia, died on May 11, 1940, of coronary occlusion, at the Army and Navy General Hospital, Hot Springs National Park, Arkansas. Dr. Hunter was born in Norfolk, Virginia, April 30, 1878. He received both his A.B. and M.A. Degrees from the University of Virginia in 1889 and his M.D. Degree from the Department of Medicine of that institution in 1901. For many years he was active in the field of roentgenology and a member of staff of the Hospital of St. Vincent de Paul, Norfolk General Hospital and Leigh Memorial Hospital. He served in the World War with the rank of Captain in the Medical Corps of the U. S. Army. He was a member and a former president of the Norfolk County Medical Society and a Fellow and Life Member of the American College of Physicians. He also held membership in the American College of Radiology, American Heart Association, American Medical Association, Virginia State Medical Society, and numerous other scientific bodies.

WALTER B. MARTIN, M.D., F.A.C.P.,  
Governor for Virginia

He was born at Cumberland Valley, Pa., and graduated from the University of Pennsylvania School of Medicine in 1898. He interned at the City Hospital of Newark, N. J., and joined the U. S. Marine Hospital Service, now the U. S. Public Health Service, in 1900. In 1913 he attained the rank of surgeon in the public health service, and of medical director in 1930. From 1908 to 1911 he was in charge of the Plague Laboratory in San Francisco, and from 1911 to 1915 Director of the Leprosy Investigation Station in Hawaii. From 1915 to 1937 he was detailed as Director of the Hygienic Laboratory, now known as the National Institute of Health, in Washington. From 1922 to 1927 he represented the United States on the Permanent Standards Commission of the Health Section of the League of Nations. In 1931 he was the recipient of the Sedgwick Memorial Medal of the American Public Health Association.

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Dr. Harold G. F. Edwards, F.A.C.P., Shreveport, Louisiana, addressed a meeting of the American Radium Society held in New York City June 10 and 11 on "An Analysis of Seven Hundred Cases of Carcinoma of the Cervix."

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Dr. Paul F. Dickens, F.A.C.P., Clinical Professor of Medicine at George Washington University School of Medicine, Washington, will have supervision of a research clinic for the treatment of heart disease, as endowed by Homer S. Cummings, LL.D., formerly attorney general of the United States. Mr. Cummings established a fund of \$1,200 per annum for five years, to be known as the Cecilia Cummings Research Fund, in honor of his wife who died from heart disease in 1939.

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Dr. John R. Williams, F.A.C.P., Rochester, N. Y., was recently awarded the Albert David Kaiser Medal of the Rochester Academy of Science in recognition of "service to the community and to the medical profession." The citation further stated that Dr. Williams "has been the leading spirit, guide and director in the establishment of the Medical Museum in the Rochester Academy of Medicine, which from its beginning has maintained a high standard of educational value for the medical profession and the public. This museum, a new department of academy activity, has already brought into active participation a large number of the medical profession who formerly had no opportunity to take part, as individuals, in the problems of education which face the medical profession."

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Dr. Harry V. Paryzek, F.A.C.P., Cleveland, was recently made President-Elect of the Ohio State Medical Association.

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Dr. Edward C. Rosenow (Associate), Rochester, Minn., gave an address on "Focal Infections" before the King County (Wash.) Medical Society at Seattle, May 28.

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The nineteenth annual convention of the American Physiotherapy Association at New York, June 23-28, was addressed by Dr. Irving S. Wright, F.A.C.P., New York City, on "Pathology of Peripheral Vascular Diseases."

requirements. The program will be further developed and announced in the early autumn.

#### BAILEY K. ASHFORD AWARD IN TROPICAL MEDICINE ESTABLISHED

In honor of the late Dr. Bailey K. Ashford, F.A.C.P., Eli Lilly & Co. established the Bailey K. Ashford Award in Tropical Medicine during the last annual meeting of the American Society of Tropical Medicine in Memphis. The Award will be made on alternate years for a total of three years and will consist of \$1,000 in cash, an engraved bronze medal and an additional amount of \$150, or as much thereof as may be required, toward traveling expenses for the recipient. The Award will be made "in recognition of demonstrated research in the field of tropical medicine, taking into consideration independence of thought and originality." The investigator must be a citizen of the United States of America and less than thirty-five years of age. He must not be associated with a commercial laboratory and need not be a member of the American Society of Tropical Medicine. Members of the American Society of Tropical Medicine may submit nominations to the Secretary of the Society in triplicate, with full information concerning the candidate's personality, training and research work. Nominations must be submitted sixty days before the annual meeting, at which the Award is to be made. The recipient will present a review of his work at the meeting.

#### SUMMARY OF THE REPORT BY THE COMMISSION ON GRADUATE EDUCATION

Important developments in the hospital internship, the hospital residency and the postgraduate educational opportunities for physicians in practice were suggested by the Commission on Graduate Medical Education, whose final report was published on June 25. The Commission, which was organized by the Advisory Board for Medical Specialties on December 4, 1937, is now bringing to a close its three year study program. Its work has been financed by national foundations and interested professional organizations.

The internship, suggests the Commission, should be considered as a basic preparation for the practice of medicine. It should round out and give practical application to the medical school course and, hence, should be closely allied to undergraduate medical education. It should prepare young physicians adequately to begin general family practice and should provide them with the essential preparation necessary to undertake further study leading to the practice of a specialty. It should not attempt to train men for the specialties directly and, therefore, the intern should not be given training in the detailed technics of the specialties.

To prepare the intern for general practice, he should have experience in internal medicine, pediatrics, obstetrics and gynecology, and surgical diagnosis, minor surgery and treatment of emergencies. Special attention in these fields should be given to preventive medicine and the care of chronic diseases, conditions of the aged and functional disturbances. The whole atmosphere should be educational in character and he should learn by example as well as precept.

The residency is defined by the Commission as a prolonged period of study in one of the special fields which can be properly classed as graduate education, whether an advanced degree is granted or not. The Commission warmly supports the recommendation of the specialty boards that adequate attention be given during the residency to the basic sciences as they relate to the various specialties. It suggests practical ways by which hospitals may provide this basic science training in their own laboratories or through arrangements with medical schools. The report suggests that there is danger that too many residencies may be developed and stresses that, in the best interests of the patient, high quality of teaching in the residency is now

Among his many other talents, Dr. Riesman was author of a long host of publications, including the following: "American Textbook of Pathology (with Ludvig Hektoen)," 1901, W. B. Saunders; "Thomas Sydenham," 1925, Paul B. Hoeber; "The Story of Medicine in the Middle Ages," 1935, Paul B. Hoeber; "Medicine in Modern Society," 1938, Princeton University Press. One of his later publications was the "History of the Medical School of the University of Pennsylvania," appearing in the "Scope," University of Pennsylvania Class of 1939. He also wrote innumerable articles for medical journals.

To the Doctorate of Medicine, which he received in 1892, were added an honorary Doctor of Science degree by Franklin and Marshall College and Doctor of Laws degree by the University of Wisconsin. He was to receive another honorary doctorate from the University of Pennsylvania at its commencement exercises June 12, 1940. He was awarded the I. P. Strittmatter medal for 1928 by the County Medical Society for "service redounding to the credit of the profession." President Clarence A. Dykstra, of the University of Wisconsin, conferred the legal degree on Dr. Riesman in 1937 as "the statesman of medicine."

Dr. Riesman was married January 20, 1908, to Eleanor L. Fleisher, a brilliant woman to whom he always directed credit for his vast mental breadth. Besides his wife, Dr. Riesman leaves two son, John Penrose Riesman, now an intern at Philadelphia General Hospital, and David, Jr., professor of law at the University of Buffalo, and a daughter, Miss Mary Riesman, who is a New York City school teacher.

By the death of David Riesman, The American College of Physicians has lost one of its great and loyal members.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

### MAJOR GENERAL JOHN TAYLOR FOTHERINGHAM

In the loss of Major General John Taylor Fotheringham, F.A.C.P., Toronto, the medical profession of Canada has lost a very distinguished member.

Dr. Fotheringham became a Fellow of the American College of Physicians in 1922 and during his active career he was a member of every organization that has stood for the advancement of the profession. He was one of the fathers of the Canadian Army Medical Corps, in which he was promoted to the rank of Major General.

Dr. Fotheringham had been in poor health for some time, but he had evinced keen interest in the developments of the present war. He was honored with a full military funeral from St. Andrew's Presbyterian Church.

Recognized for his outstanding gifts as a teacher, Dr. Fotheringham served for some years on the medical faculty of Trinity Medical School and later the University of Toronto. He was a valued member of the medical

# MINUTES OF THE BOARD OF REGENTS

SECOND MEETING, APRIL 2, 1940

The second meeting of the Board of Regents, held in connection with the Twenty-fourth Annual Session of the American College of Physicians, took place at the Cleveland Public Auditorium, Cleveland, Ohio, April 2, 1940, with President O. H. Perry Pepper presiding, with twenty-two members of the Board present and with Mr. E. R. Loveland acting as Secretary.

Secretary Loveland gave a short summary of the Minutes of the preceding meeting of the Board, which was approved as read.

Among communications were:

- (1) A report from Dr. Charles H. Cocke, Chairman of the Board of Governors, concerning the transactions of the first meeting of that Board.
- (2) A telegram from Dr. Frank J. Sladen, Director of the Postgraduate Course, "Medicine in Industry," sponsored by the College at Detroit, in which Dr. Sladen expressed his appreciation, inspiration and enthusiasm.

Dr. William J. Kerr inquired if there had been any provision for assembling notes on that particular Course for publication, feeling that the topics were of very great interest and might be of value to everyone in the College.

It was reported that the expense attached to recording these Postgraduate Courses was so great that no attempt had been made to do so.

Dr. Kerr further suggested that if any notes are available, it might be desirable to mimeograph them, or to arrange them in more permanent form for distribution, after Dr. Sladen had been consulted.

- (3) A telegram from Dr. James B. Herrick, acknowledging and expressing his appreciation of the honor of being made a Master of the College. The Secretary was instructed to reserve a room at the Headquarters' Hotel for Dr. Herrick's use on the occasion of the Convocation.

## *Unfinished Business from Preceding Meeting*

The following report was received from the Treasurer, in absentia, because of his having to conduct one of the Panel Discussions on the program:

"As of March 28, 1940, the book value of our Endowment Fund in bonds is \$78,452.50 and in stocks, \$13,650.00, totalling in the Endowment Fund, \$92,102.50.

"In the General Fund, we have in stocks invested \$82,245.00, making a total book value of our investments as of that date, \$174,347.50, which makes an increase in the total book value of our invested funds during the past year of \$2,215.22.

"Our securities have averaged an interest on investment of 4 per cent during the past year. Our operating balance of net income over expenses is \$23,939.07.

"I feel safe in reporting to you that the finances of our College are in a sound condition.

Respectfully submitted,

WILLIAM D. STROUD,  
Treasurer "

On motion by Dr. James E. Paullin, seconded by Dr. Hugh J. Morgan, and regularly carried, it was

RESOLVED, that the report of the Treasurer be accepted and filed.

both the Toronto General Hospital and Christie Street Military Hospital, and was consulting physician-in-chief for St. John's Medical Mission.

Dr. Fotheringham was married in 1891 to C. Jennie McGillivray, daughter of George McGillivray, who predeceased him. Surviving him are two daughters, Miss Helen, at home, Mrs. Ruth Kilpatrick, and one son, Donald T. Fotheringham.

"General Fotheringham's death marks the passing of one of Canada's most distinguished physicians and soldiers," said Major General John A. Gunn. "He was a great character and a marvelous lecturer. Throughout his life his service to mankind and his beloved Canada was his chief thought. Fortunate indeed were those who were privileged to come under his influence and to be regarded as his friends."

J. H. HOLBROOK, M.D., F.A.C.P.,  
Governor, Province of Ontario

### CAPTAIN CARROLL R. BAKER

Captain Carroll R. Baker, F.A.C.P., Medical Corps, U. S. Navy, died at the U. S. Naval Hospital, Washington, D. C., on April 23, 1940. Captain Baker was born at Winchester, Virginia, on April 1, 1885. He was a graduate of Jefferson Medical College, class of 1909 and served his internship at the Philadelphia General Hospital from 1910-11. He received a certificate of graduation from the U. S. Army Medical School in 1912.

Dr. Baker was commissioned an assistant surgeon in the Medical Corps of the Navy on April 10, 1914 and graduated from the U. S. Naval Medical School that year. He was promoted to the rank of lieutenant on August 29, 1916; to the rank of lieutenant commander on March 4, 1921; to the rank of commander on August 28, 1926; and to the rank of captain on February 1, 1937.

During his service in the Medical Corps of the Navy, Dr. Baker was on duty at various naval activities. He specialized in internal medicine and was an authoritative consultant in the field of cardiology. During his service career, he undertook numerous postgraduate courses in his chosen field. He served as executive officer of the Naval Medical School, Washington, D. C., from August, 1928, to July, 1931; chief of medicine on board the U. S. S. *Relief* from July, 1931, to June, 1933; chief of medicine at the Norfolk Naval Hospital, Portsmouth, Virginia, from June, 1933, to June, 1936; executive officer at the Naval Dispensary, Navy Department, Washington, D. C., from June, 1936, to March, 1937; personnel officer in the Bureau of Medicine and Surgery, Navy Department, Washington, D. C., from March, 1937, to October, 1938. At the time of his death, he was serving as chief of medicine at the Naval Hospital, Washington, D. C.

ROSS T. McINTIRE, M.D., F.A.C.P.,  
Governor for the U. S. Navy



On motion by Dr. Robert A. Cooke, seconded by Dr. James E. Paullin, and regularly carried, it was -

RESOLVED, that the report of the Committee on Fellowships and Awards be accepted.

Dr. James E. Paullin, Chairman of the Committee on Public Relations, presented a report dealing with resignations, waiver of dues, communications concerning various matters of public relations.

On motion by Dr. Paullin, regularly seconded and adopted, the resignation of one Fellow was accepted, the dues of three Associates and one Fellow were temporarily waived because of illness, the dues of one Fellow were deferred because of an accident, the request for the waiver of dues in one instance was refused, and the endorsement of the American College of Physicians was given to the American Foundation of Tropical Medicine.

Dr. Sydney R. Miller presented the revised informative booklet in proof form, and a resolution was adopted that after additional revisions had been made the proof be re-distributed to all members of the Board of Regents before being finally published.

Dr. Walter W. Palmer, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, reported a meeting of that Committee on April 1. Two matters under consideration, presented by the Editor, were the size of the volume of the ANNALS per year and the matter of the Rheumatism Review. It was the opinion of the Committee that the budget more than amply covers the publication of 2,400 pages of scientific material per year, and it was the consensus of opinion of the Committee that the ANNALS should not exceed this size, but could properly go up to that limit. In regard to the Rheumatism Review, it was pointed out that this year the Review is a long one, covering some two hundred pages which, in the opinion of the Committee, is in excess of the importance of the subject, although an admirable Review had been submitted. The Committee recommended that in the future the Review, if submitted to the ANNALS, should not exceed one hundred pages, and preferably should be under one hundred pages. Dr. Palmer added that the Committee had only admiration for the manner in which Editor Pincoffs has handled the ANNALS, and that the Journal has improved consistently in a most desirable manner.

EDITOR PINCOFFS: "To exculpate the Rheumatism Review, I might say that they themselves have written me concerning the fact that they had exceeded the proper length of this Review and were quite willing to cut it down, and asked the opinion of the Editor as to the size that it might properly be, if we wish to continue to publish it. Your Editor is very glad to have the action of the Committee on the ANNALS, and he will write them, suggesting that it be held to one hundred pages."

In answer to an inquiry from President Pepper concerning the limitation of the volume in size, Editor Pincoffs expressed his approval of the limitation suggested for the time being, but not as a permanent rule, asking that the matter be passed upon in such a way that it might be subject to some change of action on the part of the Regents later. The question of publishing the Rheumatism Review as a supplement to the ANNALS was discussed, and the Editor pointed out the disadvantages in cost and distribution that made such procedure inadvisable. The cost of publishing the current Rheumatism Review as a supplement was found to be about twelve hundred to fifteen hundred dollars, plus the additional cost of distribution. The Finance Committee had declined to approve of this expenditure.

Dr. James E. Paullin inquired why the American Rheumatism Association might not be willing to contribute something toward the publication of this Review. Editor Pincoffs said he was unacquainted with that Association's financial status, but in the original negotiations of their representatives on the publication of this Review, that Association had asked whether the College would be interested in the publication

## RECENT ANNOUNCEMENTS

## PROGRAM OF POSTGRADUATE COURSES UNDER CONSIDERATION

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Chairman of the Governors' Advisory Committee on Postgraduate Courses, in conjunction with the Regents' Committee on Educational Policy, held a meeting in New York City, June 12, for the discussion of policies, courses and dates for the schedule of Postgraduate Courses to be offered by the College during the coming year. Those present included Dr. Bortz as Chairman, Dr. Ernest E. Irons, Chicago, Dr. C. Sidney Burwell, Boston, Dr. Fred M. Smith, Iowa City, Dr. James E. Paullin, Atlanta, and Mr. E. R. Loveland, Executive Secretary of the College.

Used as a guide were the reports which had been collected from the Director of each Postgraduate Course and each registrant for the past year. Especially valuable were the suggestions of members of the College who have pursued these Courses.

The Committee is extending its study by sending a questionnaire to every Fellow and Associate of the College. In addition, it is requesting each Officer and Regent to offer recommendations for the further development of the Postgraduate Courses. As soon as the Committee has had ample opportunity to study carefully the reports from the course organizers, students who have taken the courses and the statements from the members of the College and recommendations of the College Officers, the Committee will present its final report to the Board of Regents. Thus far, many constructive comments have been received. The student doctors who have attended these courses given by the College, since their inception, have sent in most enthusiastic letters to the Executive Offices of the College. There is a rapidly growing interest and demand for Postgraduate Instruction in Internal Medicine, and it is the consensus of opinion that the American College of Physicians should display energetic leadership in this important field. It might be advisable to offer courses varying from one, two or four weeks in length; some to be offered in the autumn, others in midwinter and finally a certain number to be presented just antedating the Annual Session of the College.

There is a growing demand for courses two to four weeks in length in advanced general medicine. The most popular request, however, is for instruction in special fields such as Cardiology, Hematology, Gastro-enterology, Psychiatry, Neurology, etc. It may be that a combination course with two weeks in advanced medicine together with one or two weeks of instruction in a special field would prove attractive.

While these courses were created originally, solely for the members of the College, several men on the Committee have signified their interest in admitting to the courses qualified non-members of the American College, who are recommended by an Officer, Regent or Governor of the College. With the admission of carefully selected non-members, the College would, by this movement, assist men aspiring to Fellowship in the American College to attain advanced training in Internal Medicine.

If the American College of Physicians offers Postgraduate Courses at different seasons of the year, it may be possible for men to take more than one course per year. Coördination of the courses offered should be of such a nature that, over a period of three or four years, the student who desires may receive the equivalent of a year's study in advanced Internal Medicine, ordinarily leading to some degree.

There was a consensus of opinion that the College has been primarily instrumental in setting up the advanced requirements for the practice of Internal Medicine, not only through its own standards of admission, but through the examinations of the American Board of Internal Medicine, and that, therefore, the College has an obligation to see that facilities shall be available to enable men to meet such advanced

were simply by the President in his wisdom. It is quite within the power of this Board to state that these appointees to the Conference Committee and the Committee on Postgraduate Education itself may be drawn from the Regents, the Governors, or the membership at large, and then the matter may be left to the incoming President's duty to make these appointments."

On motion by Dr. Hugh J. Morgan, seconded by Dr. James D. Bruce, and carried, it was

RESOLVED, that appointments from the American College of Physicians to the Conference Committee on Graduate Training in Medicine be left to the incoming President, Dr. James D. Bruce, who may appoint men to these positions from the College at large, including the Governors.

Dr. Ernest E. Irons, speaking to the motion, said that Dr. Morgan had done an exceptional job thus far, and it should be hoped that the incoming President would be able to convince Dr. Morgan, in spite of his moral responsibility to his school, to continue on that Committee, and that the College needs Dr. Morgan's supervision and drive to carry through the College plans.

Dr. James D. Bruce also complimented Dr. Morgan's work, and expressed the hope that he would agree to continue to serve.

President Pepper reiterated Dr. Irons' sentiments, commending Dr. Morgan's efficiency and skill on this Committee.

Dr. Morgan then was asked to re-present the suggestion concerning a formal certificate of attendance for the Postgraduate Courses.

On recommendation and motion by Dr. Hugh J. Morgan, seconded by Dr. James E. Paullin, and regularly carried, it was

RESOLVED, that the College, through its Executive Offices, shall issue to each physician attending its postgraduate Courses a formal card attesting to his having enrolled and attended a specific Postgraduate Course sponsored by the College.

Furthermore, it was agreed that this card could be presented by Associates as a helpful credential when said Associates are qualifying for advancement to Fellowship. It was also directed that this card be sent to all men who have taken the Courses in the past, as well as for the current year.

Dr. Morgan again brought up the matter of the policy of the College relative to research and clinical fellowships. He suggested that the Regents should first decide how much of the College funds shall be put into fellowships each year, and then determine how much shall be segregated to research fellowships and how much to clinical fellowships. He felt that the present Research Fellowships have been extended from year to year somewhat haphazardly without actually confining the limit of the amount of money to be spent. He emphasized the need of fellowships for training of men to go into practice, to extend the number of opportunities that there are in the country for what actually amounts to residency experience in Internal Medicine.

President Pepper recommended that the incoming Committee on Fellowships and Awards and the incoming Committee on Finance should be asked to consider this recommendation before the preparation of the budget for 1941.

On motion by Dr. James D. Bruce, seconded by Dr. Sydney R. Miller, and carried, it was

RESOLVED, that the President be instructed to send a telegram to the Surgeon Generals of the Army and Navy, thanking them for having assigned Officers from their respective Services to give the Symposium on Military Medicine on the College program April 1.

more important than a large increase in the number of residencies. The essentials of a satisfactory residency are listed in some detail, although the Commission takes pains to point out that it does not wish to standardize residencies or put them in a strait jacket.

Postgraduate education the Commission defines as study intended to keep a physician abreast of his chosen field of practice but not intended to equip him to enter a new field. Separate and clearly defined types of work are recommended for general practitioners and for specialists. While there has been a marked and rapid increase in interest in the field of postgraduate medical education, there is still need for its further extension and for improvement in the type of opportunities offered. The report points out the advantages and disadvantages of the various types of training now provided.

The effect of the work of the specialty boards upon the practice of medicine is discussed in the report, which points out that these boards have provided a well defined yardstick for measuring an individual physician's competence in his specialty. Men in the specialties have been certified so rapidly that it soon will be possible for the great majority of the people of this country to have access to the services of certified specialists.

The entire report stresses the value of adequate training and points out that this will be reflected in improved care of patients.

this committee to have the sole duty of organizing the Postgraduate Courses, their decisions to have the approval of the Regents' Committee on Educational Policy.

President Pepper, after reading announcements, addressed the Board as follows:

"It is the sad duty of the President to state that to the best of his knowledge this meeting terminates the service on the Board of Dr. Sydney R. Miller and Dr. Ernest B. Bradley. Both of these gentlemen have been Presidents of the College and have served the College faithfully and long, and only the necessities of the Constitution and By-Laws prevent their continuance. We see their departure from this Board with great regret.

"This meeting terminates my presiding over these meetings, and although I will, of course, be with you, I want to express very briefly my sincere appreciation of your coöperation. Any man of you who has had the slightest chance to coöperate has done so in the fullest extent. I can't imagine a President having things made any easier for him than your efforts have made things for me. The Presidency of this College is a sinecure when they have committees such as those which you all represent.

"I thank you, every one of you."

Adjournment.

Attest: E. R. LOVELAND,  
*Executive Secretary*

### THIRD MEETING, APRIL 5, 1940

The third meeting of the Board of Regents, held in connection with the Twenty-fourth Annual Session of the American College of Physicians, was held at the Cleveland Public Auditorium, Cleveland, Ohio, April 5, 1940, with Dr. James D. Bruce, President, presiding, fifteen members of the Board present and Mr. E. R. Loveland acting as Secretary.

The Secretary presented an abstract of the transactions of the preceding meeting of the Board in accordance with provisions of the By-Laws.

The meeting proceeded to the election of the Treasurer and the Secretary-General for 1940-41.

On motion by Dr. James E. Paullin, seconded by Dr. Reginald Fitz, Dr. William D. Stroud was nominated for reelection as Treasurer.

On motion by Dr. D. Sclater Lewis, seconded by Dr. James E. Paullin, and carried, it was

RESOLVED, that nominations for Treasurer be closed and the ballot cast by the Chairman.

Dr. Bruce announced Dr. William D. Stroud duly reelected Treasurer for 1940-41.

On motion by Dr. James E. Paullin, seconded by Dr. Henry M. Thomas, Jr., Dr. George Morris Piersol was nominated for reelection as Secretary-General.

On motion by Dr. Charles H. Cocke, seconded by Dr. William J. Kerr, it was

RESOLVED, that nominations for Secretary-General be closed and the ballot cast by the Chairman.

President Bruce announced Dr. George Morris Piersol reelected Secretary-General for 1940-41.

The Executive Secretary, Mr. Loveland, distributed mimeographed copies of the financial report for 1939 and copies of the consolidated budgets for 1940.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, reported as follows:

"At the last meeting of the Board of Regents, December, 1939, the Board of Regents appointed five Research Fellows for 1940-41. Among them was Dr. Richard Lyons, who has informed the Committee that he would be unable to accept the fellowship because of another opportunity. Apologetic letters had been received from his sponsors at the University of Michigan, who apparently felt that this other opportunity was so good that Dr. Lyons was justified in taking it. Other members of the Committee had been circularized concerning the appointment of another Research Fellow in Dr. Lyons' place. Other applicants, in the opinion of the Committee members, were not of such caliber to justify their appointment. Soon thereafter word was received from Dr. Hugh J. Morgan, of Nashville, Tenn., concerning Dr. Homer Swanson, who has been working at Vanderbilt University, but whose arrangements could not be carried out further without a fellowship grant. Dr. Morgan was invited to present to the Committee Dr. Swanson's qualifications as a possible Research Fellow, and the Committee at this time request Dr. Morgan to present the candidate's qualifications to the Board of Regents."

Dr. Hugh J. Morgan presented all salient details concerning the preparation, interest, qualifications and history of the candidate.

On motion by Dr. Barr, seconded by Dr. William J. Kerr, and after general discussion of the candidate's age, date of graduation and other qualifications, the following resolution was unanimously adopted:

RESOLVED, that Dr. Homer Swanson shall be awarded a Research Fellowship of the American College of Physicians in the amount of \$1,800.00 for a period of one year, beginning July 1, 1940.

It was thereafter pointed out that this was the first occasion on which the College had awarded a Research Fellowship in Neurology, an act that met with general approval.

The Committee on Fellowships and Awards presented adverse recommendation in regard to a request for a subsidy of \$150.00 for work contemplated in Hematology at the University of Louisville, based upon the fact that the College had adopted no policy concerning subsidies and that the Committee believed that in this instance a subsidy might be obtained from the Council on Pharmacy and Chemistry, or through another source of the American Medical Association or elsewhere.

The matter was generally discussed, and there appeared to be no definite feeling that the College should embark on the subsidizing of individual research.

Dr. Ernest B. Bradley raised the question as to whether the Committee had ever considered whether all Research Fellows require as much as \$1,800.00 for their year's work?

Dr. Francis G. Blake stated that in the National Research Council funds are somewhat more liberal in amount, the minimum being \$1,800.00. Since less funds have been available, after careful investigation, the Council has given some awards of not more than \$1,600.00 for a single man in communities in which it was felt that he could get along adequately on that amount; \$2,300.00 for a married man; with \$200.00 more added for children. Dr. Blake felt that in many instances, \$1,600.00 has proved quite adequate for younger men.

Dr. David P. Barr pointed out that the regulations of the College Committee on making awards provide that the man must be accepted by the institution in which he wishes to work, and that the institution agrees to supply such things as are necessary for the conduct of the work.

*Advisory Committee on Postgraduate Courses*

Edward L. Bortz, Chairman  
 C. Sidney Burwell  
 Ernest H. Falconer  
 Fred M. Smith  
 James J. Waring

(This Committee, appointed by the Chairman of the Board of Governors in consultation with the Chairman of the Board of Regents, is a new committee as constituted by the Regents on April 2, 1940.)

*Committee on Fellowships and Awards*

David P. Barr, Chairman	(reappointed)
Francis G. Blake	(reappointed)
Ernest E. Irons	(reappointed)
Jonathan C. Meakins	(reappointed)
Henry M. Thomas, Jr.	(new appointment)

*Committee on Finance*

Roger I. Lee, Chairman	(1943) (reappointed)
Charles T. Stone	(1941)
O. H. Perry Pepper	(1942) (new appointment)

*Committee on Public Relations*

James E. Paullin, Chairman	(1943)
T. Homer Coffen	(1941) (new appointment)
Gerald B. Webb	(1942) (new appointment)
Henry M. Thomas, Jr.	(1944) (new appointment)
James D. Bruce	Ex Officio

*Committee on Revolving Loan Fund*

Maurice C. Pincoffs, Chairman	(reappointed)
Egerton L. Crispin	(reappointed)
Roger I. Lee	(reappointed)

*Committee on Scientific Exhibits (present committee continued)*

Francis G. Blake, Chairman  
 Robert A. Cooke  
 D. Sclater Lewis

*Committee on Survey and Future Policy*

James Alex. Miller, Chairman	(reappointed)
Charles H. Cocke	(reappointed)—Chmn., Bd. of Governors
Roger I. Lee	(new appointment)—Chmn., Finance Com.
Jonathan C. Meakins	(reappointed)—Amer. Bd. of Int. Med.
Hugh J. Morgan	(reappointed)—Com. on Educational Policy
George Morris Piersol	(reappointed)—Chmn., Credentials Com.
Maurice C. Pincoffs	(reappointed)—Editor, A. I. M.

simply as a Review in the ANNALS, stating that its committee felt they had no funds otherwise to publish it and were offering it to the College first. Dr. Pincoffs expressed the opinion that if the Review is cut down to one hundred pages, it is just as worthy for free publication in the ANNALS as any other material. This particular article, or review, has led to more calls from outsiders for copies of the ANNALS than any other article. Dr. Pincoffs also stated that the Archives of Internal Medicine not only publish some reviews free, but pay the men who make the reviews.

In the discussion that followed, it was brought out that the authors of the Rheumatism Review have the College printers run off several additional copies bound as a single publication, and that they distribute them to the members of their Association and also have them for sale. In this way the authors are saved the expense of typesetting and can secure copies at very reduced rates. If these are put on sale they naturally can be distributed at considerably less cost than can the College distribute copies of the ANNALS itself in which the Reviews appear.

On motion by Dr. Hugh J. Morgan, seconded by Dr. Ernest B. Bradley, and regularly carried, it was

RESOLVED, that the report of the Committee on the ANNALS OF INTERNAL MEDICINE be accepted.

President Pepper called upon the Chairman of the American Board of Internal Medicine for a report.

DR. ERNEST E. IRONS: "The American Board has now issued 2,158 certificates. Of these, 358 were certified by examination. In addition, 111 candidates were examined on Saturday and Sunday last. A brief review of the four years' work of the Board was presented yesterday. Our finances are in a healthy condition. Our bank balance was \$18,548.14 on January 1, 1940. We have no financial obligations outstanding. Negotiations are proceeding satisfactorily in the matter of providing for recognition of medical sub-specialties in the work of the Board. A cordial working arrangement between the College, as represented by the Committee on Graduate Medical Education under Dr. Morgan, the Council on Medical Education of the American Medical Association, and the Board of Internal Medicine has been worked out and is in operation."

President Pepper called for a continuation report from the Committee on Postgraduate Education:

DR. HUGH J. MORGAN: "I wish to withdraw certain suggestions which were made at our preceding meeting relative to the reorganization of the Postgraduate Committee of the Regents. I would like you to consider the advisability of delegating the authority in this meeting to such worthy representatives of the College who are to participate in the work of the Conference Committee of the Council on Medical Education and Hospitals, and that representatives of the College may be appointed, perhaps, outside of the Board of Regents. I think there may well be two men in the College—Regents, Governors or Fellows—who could represent the College and do a much better job on this Conference Committee than I will be able to do. I don't want to go on this Conference Committee as a rubber stamp for the Council, and I am afraid that is what will happen, unless we get representatives on that Committee who are interested and who have the time to put in a lot of solid work. I hope it can be made possible for the College to be represented by someone other than the Chairman of the Postgraduate Committee on this Conference Committee."

PRESIDENT PEPPER: "The matter brought up by Dr. Morgan is entirely within the authority of the Regents. The Postgraduate Committee is a creature of this Board, and the appointments to the Conference Committee were not ex officio, but



President Bruce then asked for suggestions concerning the election of a General Chairman for the 1941 Session and the selection of dates. He suggested that it might be quite appropriate for Dr. Roger I. Lee, Boston Regent, himself and others to confer concerning the appointment of the General Chairman.

On motion by Dr. O. H. Perry Pepper, seconded by Dr. Reginald Fitz, and regularly carried, it was

RESOLVED, that the authority to appoint the General Chairman and select the dates for the 1941 meeting be vested in the President in conference with Dr. Roger I. Lee.

Adjournment.

Attest: E. R. LOVELAND,  
*Executive Secretary*

By resolution, one Associate and two Fellows were dropped from the College Roster because of delinquency of two years' or more standing, action being taken in accordance with provisions of the By-Laws.

Dr. George Morris Piersol reminded the Board that no action had yet been taken on the recommendation of the Committee on Postgraduate Education in regard to an appointment of a committee of the Board of Governors to organize and direct the Postgraduate Courses, this duty being delegated from the Regents' Postgraduate Committee acting in an advisory capacity. Dr. Piersol said that the Regents' Committee would be very glad to have a Committee of Governors to take over the organization, extension and expansion of these Courses, but that they can hardly do it without authority from the Board of Regents. It was suggested that the Regents' Committee be called the Committee on Educational Policy and the Governors' Committee be called the Advisory Committee on Postgraduate Courses.

Dr. Morgan asked for a discussion of the practicability of such a plan by the Executive Secretary, Mr. Loveland.

MR. LOVELAND: "I am sure it would be practicable for the Regents' Committee on Postgraduate Education to be a Committee on Policy, the real authoritative committee for contacts with the Conference Committee on Graduate Training in Medicine, the Advisory Council on Medical Education, Licensure and Hospitals, the Council on Medical Education and Hospitals of the American Medical Association, etc., and for this committee, through the Board of Regents, to delegate to a Committee of the Board of Governors the organization and general direction of the Postgraduate Courses. The Board of Governors meets but once a year. Under the Constitution, it has no authority for appropriations. Therefore, the general supervision, including official appropriations and authorization must remain with the Board of Regents. The Board of Governors may very properly have a committee whose sole and primary duty is the conduct of the Postgraduate Courses, but it is recommended that the Chairman of that committee, the working Chairman, be near Philadelphia and the Executive Offices. There are many problems that arise in the course of registering the physicians for these Courses, and it would be a matter of great convenience in their administration to have the Chairman of the committee available for personal conference and advice. Furthermore, there is a crying need to have these Courses organized and announced much earlier in the year. The December meeting of the Board of Regents is too late, especially when one considers that it takes several weeks to get the copy of the detailed courses from each director, to have the bulletins printed and distributed. The Advisory Committee on Postgraduate Courses should have certain authority delegated to it by the Board of Regents, such as to proceed in the preparation of courses immediately after our Annual Session, and to be ready to announce them early in the autumn."

DR. BRUCE: "As I understand it, the Committee on the Board of Governors should assume the responsibility for advising the Regents' Committee; that the final authority, financial and otherwise, shall rest with the Board of Regents, and the Committee of the Board of Governors shall act as an activating or advisory committee, to set up such courses as it be most appropriate."

On motion by Dr. Hugh J. Morgan, seconded by Dr. George Morris Piersol, and regularly carried, it was

RESOLVED, that the Board of Regents shall have a Committee on Educational Policy, consisting of three members appointed by the President, and that the Board of Governors shall have an Advisory Committee on Postgraduate Courses, appointed after conference between the President and the Chairman of the Board of Governors,

the extensive use of the plasma treatment of shock in wartime. Being dry, the plasma could be contained in small metal ampoules or cans to facilitate shipment and handling.

The second problem solved by desiccation is the production of an ideal hypertonic solution for intravenous use, namely, concentrated plasma or serum. When the dried plasma is dissolved in distilled water any desired concentration from four times normal down to normal or even more dilute than normal (hypotonic) can be made as desired. This not only permits unusual flexibility, but also opens up new therapeutic possibilities in the regulation of fluid balance, blood volume and pressure, as yet only partially explored. Furthermore enough protein can be given as concentrated plasma with a large syringe (100 c.c.) at 12 to 48 hour intervals to sustain blood protein levels when food cannot be taken by mouth or when for other reasons protein levels are not maintained as in cirrhosis, cachectic states, etc.

These therapeutic advantages, peculiar to the intravenous use of human plasma or serum of various concentrations, have not as yet been generally appreciated. This has been due in a large measure to the limited supply of such plasma. Two reasons for this limitation have been apparent: first, the difficulty of obtaining a sufficient amount of blood, and second, the expense or complexity of available desiccating processes by which storage and concentration can be accomplished. Accordingly, it is the purpose of this paper to describe a new desiccating process employed at Baylor University Hospital for this particular use, and to report its routine operation in connection with a Blood Bank, to provide an adequate supply of plasma of any desired concentration up to four times normal.

In reviewing the development of desiccation of biological substances, it is of interest to note that definitely improved methods of desiccation have been followed by new and multiplied uses. On this basis two periods can be made out. In the first, desiccation was used on a very small scale for a limited amount of research and special teaching. In the second, research and teaching uses were expanded and desiccation was applied to preservation of convalescent sera in a few large centers. A third period, marked by the general preservation and use of whole plasma of various concentrations attained by means of desiccation, seems to be foreshadowed by the growing appreciation of the value of supporting blood protein levels, and of the use of concentrated plasma for its hypertonic effects.

Shakell<sup>3</sup> in 1909 discovered the basic principle of vacuum desiccation from the frozen state, which is so essential to the production of a highly soluble product with retention of its original properties. He also encountered the basic problem of this type of dehydration, namely, how to deal with the huge volume of water vapor released from only a few cubic centimeters of ice under the high vacuum conditions necessary to this process, a volume far too great for any pump to handle. Shakell solved this problem by chemical absorption and set a precedent followed by many investigators since. His choice of sulphuric acid for a desiccant as well as the design of his machine

The Executive Committee for 1940-41 was elected and constituted as follows:

James D. Bruce, Chairman	President
Roger I. Lee	President-Elect
George Morris Piersol	Secretary-General
William D. Stroud	Treasurer
Francis G. Blake	(new election)
Reginald Fitz	(reëlected)
Hugh J. Morgan	(reëlected)
O. H. Perry Pepper	(new election)
Maurice C. Pincoffs	(reëlected)

In accordance with directions and regulations of the Constitution and By-Laws, or of specific resolutions governing committees, the following were appointed by President James D. Bruce:

*Committee on Advertisements and Commercial Exhibits*

George Morris Piersol, Chairman	(reappointed)
Sydney R. Miller	(new appointment)
William D. Stroud	(reappointed)

*Committee on the Annals of Internal Medicine*

Walter W. Palmer, Chairman	(1943) (reappointed)
David P. Barr	(1941)
Reginald Fitz	(1942)

*Committee on Constitution and By-Laws*

Ernest E. Irons, Chairman	(1942)
J. Morrison Hutcheson	(1941)
William J. Kerr	(1943) (new appointment)

*Committee on Credentials*

George Morris Piersol, Chairman	(1943) (reappointed)
James G. Carr	(1941) (new appointment)
Robert A. Cooke	(1942) (new appointment)
Charles H. Cocke	(1941)
J. Owsley Manier	(1942)
William B. Breed	(1943) (reappointed by Board of Governors)

*Committee on Educational Policy*

Hugh J. Morgan, Chairman
Charles H. Cocke
Ernest E. Irons

(This Committee is the result of a reorganized plan as provided in the Minutes of the Board of Regents on April 2.)

*Advisory Council on Medical Education, Licensure and Hospitals*

Hugh J. Morgan	(reappointed)
James H. Means	(reappointed)

*Conference Committee on Graduate Training in Medicine*

Hugh J. Morgan	(reappointed)
O. H. Perry Pepper	(new appointment)

nephrosis. Ravdin<sup>14</sup> employed lyophil serum both concentrated and normal for the prevention and correction of hypoproteinemia after gastric operation. However, he hesitated to recommend it because of the frequency with which he encountered reactions.

The exact method of preparation of the serum used in the above reports was not always stated; presumably a low temperature condenser method was employed. At best, this method is too expensive for general use. A very much cheaper process, the Cryochem, was described by Flosdorf and Mudd<sup>15</sup> in 1938. They resorted to chemical absorption but with much greater success than earlier workers because of their choice of a much more suitable chemical, specially prepared anhydrous calcium sulphate, known as "Drierite." This process, although the most economical to date, still has serious drawbacks to be discussed later. A recent work on desiccation is that of Greaves and Adair.<sup>16</sup> They employ the older method of cold surface condensation of the water vapor but make important contributions to the study of the thermodynamics of desiccation. Bauer and Pickels<sup>17</sup> described a modification of the Flosdorf and Mudd Lyophil Machine in which they desiccated yellow fever virus. Continued frozen condition of the virus was assured by keeping it during processing in a hardening cabinet at  $-18^{\circ}$  C.

#### THE ADTEVAC PROCESS: DESCRIPTION OF PRINCIPLE AND OPERATION

In attempting to build a machine at Baylor to operate with the Blood Bank, and suitable for the desiccation of large quantities of normal plasma as well as convalescent serum, we early realized the need, not for a different type of machine, but for an entirely new process. As a result, the older methods of cold surface condensation and chemical action were abandoned and experiments with a physical process, adsorption, were undertaken. The entirely new problems encountered in its use for this purpose were satisfactorily handled by the application of the principles of thermodynamics and proper engineering practice and design.

Like other processes, the one herein reported accomplishes desiccation from the frozen state by means of vacuum and removal of water vapor. The removal of water vapor, however, is accomplished in a manner entirely new in this field, namely by controlled adsorption. The operation can best be explained by reference to a simplified diagram of the machine, figure 1. The serum is contained in an ampoule (1) attached by a compression joint (2) and flexible metal bellows (3) to a vacuum tank (7) in which the adsorbent (8) is placed. When the vacuum pump (9) has sufficiently reduced the pressure in the system, rapid boiling occurs in the serum as dissolved gases, such as  $O_2$ ,  $N_2$ ,  $CO_2$ , etc., are released. During this phase the flexible metal bellows (3) permits lowering of the ampoule. The violence of the degassing process is controlled by admitting small amounts of air through a valve (4). This air is sterilized by passage through a suitable filter (5) and sterility maintained in the ampoule and manifold by properly locating a

*Consulting Committee on Annual Sessions*

James D. Bruce, Chairman  
 William B. Breed  
 O. H. Perry Pepper  
 Howard T. Karsner  
 William J. Kerr  
 John H. Musser

*House Committee*

William D. Stroud, Chairman	(reappointed)
T. Grier Miller	(reappointed)
Harry B. Wilmer	(new appointment)

The Regents were reminded that reappointments had already been made to the *American Board of Internal Medicine* at the Regents' meeting, March 31, 1940, which constituted the current board, so far as the American College of Physicians' appointments are concerned, as follows:

William S. Middleton	(1941)
Louis Hamman	(1941)
David P. Barr	(1942)
Jonathan C. Meakins	(1943)
G. Gill Richards	(1943)

President Bruce requested more time to consider appointments to the Committee on Nominations, which he stated would be announced shortly after the Session closed.

President Bruce called for the presentation of communications and invitations for the 1941 Session of the College.

The Secretary, Mr. Loveland, read invitations from Kansas City, the University of Chicago, Philadelphia, Rochester, Baltimore, San Francisco and Boston. These invitations had been initiated by physicians on invitations in the cities named, and for the most part included letters from the deans of medical schools, secretaries and officers of local medical societies, and from such civic agencies as the Chambers of Commerce, Mayors, Governors, etc.

Dr. Roger I. Lee spoke on the invitation from Boston, saying that the Boston profession is very anxious to have the College accept the invitation, and that he felt Boston has all necessary facilities, including especially the clinical facilities. Immediately Dr. Lee moved that the College accept the Boston invitation. The motion was seconded by Dr. James E. Paullin and was opened for discussion.

Dr. Charles H. Cocke, Chairman of the Board of Governors, reported that that Board had also considered the various invitations, and would strongly support that from Boston—in fact, unanimously.

The motion was put to vote and it was unanimously

RESOLVED, that the American College of Physicians shall accept the Boston invitation for its 1941 Annual Session.

Dr. William J. Kerr reminded the Board that San Francisco is ready and strongly desirous of a careful consideration of its invitation for a meeting in San Francisco again in the near future. He said that they would be very happy to have the College think of San Francisco for 1942, and that in the meantime a more formal and complete invitation will be prepared.

minimal quantities of air. When the point is reached where the air is eliminated and the system entirely filled with water vapor \* a definite relation of temperature to pressure is found. This is according to the well known laws governing the pressure temperature relation of saturated steam or water vapor.

It is well known, for example, that the temperature in a steam sterilizer is related directly to the steam pressure and to the pressure only. Less familiar is the fact that the same relation in respect to water vapor holds as the pressure is reduced well below atmospheric levels. Below atmospheric levels the vacuum is conveniently expressed as absolute pressure in terms of the height of a column of mercury, as read by a special instrument. For example, at 9.1 mm. of mercury the temperature of saturated vapor is  $10^{\circ}$  C. This also means that at this pressure water boils at  $10^{\circ}$  C. At pressures below 4.5 mm. the temperature will be below the freezing point of water and under these conditions water in the system will have to be either in the form of ice or vapor.

This temperature pressure relationship explains why spontaneous freezing occurs in the ampoule when the absolute pressure falls below 4.5 mm. of mercury. It also indicates why the plasma remains frozen, with vaporization directly from the ice crystals continuing until dryness is attained. It is essential to note that once the water becomes vapor it must be regarded as a gas, subject to the laws of gases. As a consequence, we find that under the conditions of operation, for instance at an absolute pressure of 181 microns, the volume of water vapor resulting from the evaporation of one liter (one kilo) of water would be 4,670,930 liters. This indicates that no vacuum pump of reasonable size could remove the water vapor at sufficient speed. Failing to do this, the high vacuum necessary for the process obviously could never be attained, and freezing could not occur. Consequently, the necessity became apparent for some provision other than the vacuum pump, to remove the water vapor in the process.

In searching for a suitable substance to bind water vapor an adsorbent such as silica gel was suggested by two outstanding properties demonstrated by its use in the field of air conditioning. The first of these is its ability to take up very large quantities of water vapor up to 30 per cent in weight or more, and the second is the relative permanence of such substances. Since the union to water is physical, no appreciable deterioration occurs, upon drying off the water by heat, cooling and re-using. With reasonable care the adsorbent can be used indefinitely.

At this point a brief consideration of adsorption seems desirable. Adsorption is defined as the concentration of substances out of liquid or gaseous mixtures on the surfaces of liquids or solids. Many solid materials such as silica gel, charcoal, activated alumina, ferric hydroxide gel and others possess the power to adsorb gases and vapors to an unusual degree. According to

\* Due to inevitable small leaks, a perfect saturated vapor condition is never actually attained. For practical purposes, however, it may be so considered.

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## A NEW AND ECONOMICAL DESICCATING PROCESS PARTICULARLY SUITABLE FOR THE PREP- ARATION OF CONCENTRATED PLASMA OR SERUM FOR INTRAVENOUS USE: THE ADTEVAC PROCESS \*

By JOSEPH M. HILL, M.D., and DAVID C. PFEIFFER, M.E., *Dallas, Texas*

A PRACTICAL and inexpensive desiccation process is vital to the development of the widespread use of plasma and serum (ordinary or convalescent) because it solves two main problems in this field. First, storage difficulties practically cease to exist. While it is true that liquid serum may be stored, even without refrigeration as emphasized recently by Levinson,<sup>1</sup> there is no margin of safety. Contamination with but one bacterium could quickly spoil this excellent culture medium if stored without refrigeration. Also at room temperatures, the antibodies, prothrombin and other valuable biological properties rapidly deteriorate. By contrast, serum stored in the dry so-called lyophilic form will not support bacterial growth at any temperature, and in addition all the biological properties are preserved to a remarkable degree.

Under optimum conditions, no limit for the preservation of antibodies has yet been determined but it appears almost certain that immune sera can be preserved for many years. Even the highly labile complement has been successfully preserved by Kolmer<sup>2</sup> for 13 months. The possibility of almost indefinite preservation of potent convalescent sera, accomplished by an inexpensive method, brings the serum center and all its advantages within the scope of the average large hospital. With the necessity for rapid "turn-over" of serum eliminated, such serum centers need not be limited to great centers of population as in the past. The safe, yet indefinitely long storage of whole plasma, possible in the dehydrated state, should also make practical

\* Read at the annual meeting of the Texas Club of Internal Medicine, Dallas, February 16, 1940.

From the Department of Pathology, Hospital Laboratory Division, Baylor University College of Medicine.



vapor one molecule deep on the surface of the solid. The second effect consists of the formation of a second layer of vapor of variable thickness held by the molecular attraction between the solid and the vapor, the thickness depending upon the strength of the attraction. The third effect is that of collection on the surface of submicroscopic capillary openings, of the more or less condensed layer of vapor. The three effects are cumulative, and adsorbing agents possess them in varying proportions to a greater or less degree. The amount of vapor adsorbed is, therefore, a function of the vapor pressure. It is evident that it must be also a function of the temperature. Change in either vapor pressure or temperature alters what may be called the "ease of condensation" of the vapor.

Reference to figure 2 shows that the capacity of a typical adsorbent (silica gel) to adsorb water vapor is dependent not only upon the vapor pressure to which the gel is exposed, but also upon the temperature of the gel itself. At low temperatures the capacity is greatly increased, while rising temperatures in the adsorbent are accompanied by diminished capacity to take up water vapor. This fact is of great practical importance since a definite amount of heat is liberated when the adsorbent takes up water called the heat of adsorption, which by raising the temperature of the adsorbent tends to reduce its capacity for further binding of water. In our machine this heat is removed by a small standard refrigeration unit. The actual transfer of heat can easily be accomplished in several ways according to the engineering design, by providing suitable metal pathways.

By this arrangement of refrigeration and heat transfer it is not only possible to remove the heat generated during the operation of the process, but it is also possible to cool the adsorbent and improve its effective capacity. Furthermore, since the greatest flow of vapor occurs early in the process, just prior to freezing, with consequent generation of unusual amounts of heat, it is best to pre-cool the adsorbent to accommodate this temporary heavy load.

If desired the plasma may be pre-frozen in the ampoules. This of course is desirable when desiccating small amounts such as are employed in storing complement, cultures, and in other laboratory uses.

As Greaves and Adair<sup>16</sup> have pointed out, the desiccation time can be greatly shortened by applying heat to the substance being processed, especially in the earlier stages. This heat is translated into an increased flow of vapor from the frozen surface, but if this increased flow can be removed rapidly by the desiccant the pressure in the ampoule need not rise significantly and as a consequence the temperature will be substantially unchanged. In the Adtevac process advantage can be taken of this fact due to its ability to take up large volumes of water vapor rapidly. This represents a definite advance in speed of processing since earlier methods were easily overloaded when acceleration of evaporation by heat was attempted, as Greaves and Adair<sup>16</sup> showed.

definitely limited its use. Other workers using chemical absorption were Elser, Thomas and Steffen,<sup>4</sup> and Greaves and Adair<sup>5</sup> who improved machine design but found their methods severely restricted by the characteristics of the chemicals used. In general these difficulties were insufficient speed of absorption, dilution, scum formation, or other changes retarding the pickup of water vapor as the process proceeded. These difficulties increased with any increase in size of the apparatus. This, and the expense involved in using new desiccant each time, limited the use of these processes. In quality, however, satisfactory products were obtained. Elser, for example, was able to preserve cultures of meningococci and gonococci in viable condition for 18 years.

Greater possibilities in the field of desiccation were opened up when Elser introduced the use of very cold surfaces for the condensation of water vapor as ice. He first used CO<sub>2</sub> snow ( $-70^{\circ}$  C.) then mechanical refrigeration with resulting temperatures of  $-34^{\circ}$  C. These low temperatures were held in a refrigeration line within the manifold and resulted in a flow of water vapor from the frozen material being processed, to the refrigerator tubing where it was bound as super cold ice. This vapor flow was a result of the lower vapor pressure of the ice on the tubing in comparison to the vapor pressure of the ice in the ampoule. Elser also appears to have been first not only to employ manifolds with compression joint connections, but also to process large quantities of biologicals in original containers and to vacuum seal directly from the machine. Flosdorf and Mudd<sup>6</sup> employed similar principles in their machine, using dry ice in methyl cellusolve for the condenser refrigerant and effected an improvement by removing the cold surface from the manifold to a connected condenser chamber.

These improvements were followed by reports of clinical use of convalescent serum preserved and concentrated by the technic of Flosdorf and Mudd. McGuiness, Stokes, and Mudd<sup>7</sup> described good results in the use of convalescent sera preserved by desiccation. In a large series of cases results were found to be comparable with regular liquid serum, both in prophylaxis and treatment, but five fairly severe febrile reactions were observed. Stokes, Mudd, Arddy, Eagle, Flosdorf, and Lucchesi<sup>8</sup> made a similar report of the effective use of convalescent serum preserved by desiccation. Mudd, Flosdorf, Eagle, Stokes, and McGuiness<sup>9</sup> reported not only additional information on the keeping qualities and use of desiccated convalescent serum, but also detailed their technic of collections and filtration for intravenous use.

The value of the hypertonic qualities of concentrated serum was recognized in the experimental work of Bond and Wright<sup>10</sup> in the treatment of shock by its intravenous administration. Hughes, Mudd, and Strecker<sup>11</sup> reported the advantage of intravenous concentrated serum for the reduction of increased intracranial pressure. The effect of concentrated serum on the spinal fluid pressure was studied further in animals by Wright, Bond, and Hughes.<sup>12</sup> Aldrich, Stokes, Killingsworth, and McGuiness<sup>13</sup> used concentrated serum with good results to initiate diuresis in the treatment of

paper. Another test of quality, however, is the determination of residual dryness according to the method of Flosdorf and Webster. They state that a residual moisture of 1 per cent or less is satisfactory for biological use. We have found that the possible dryness obtained varied with the moisture load imposed on the adsorbent. However, even with maximum loads it was found possible to attain moisture analyses of less than 1 per cent. However, when plasma was further subjected to desiccation with a new dry charge of adsorbent substituted for the already used, thus operating the process in two stages,\* the residual moisture is almost too small for accurate analysis. For example, under these conditions moistures of .03 per cent and less are obtained.

The chief advantage of the new process is the economy of operation. Unlike earlier methods using chemical absorption, the Adtevac process does not require the frequent replacement of expensive desiccants. Furthermore, much larger quantities of water for a given weight of adsorbent can be taken up at one operation. This emphasizes the disadvantages of chemical union with water vapor as contrasted with adsorption, since by our method as high as 14 per cent capacity has already been realized. Theoretical considerations indicate a considerably higher capacity can be attained under optimum conditions.

The limited space usually allotted to hospital laboratories makes it desirable to have a maximum capacity for unit size. In this respect the new adsorption process enjoys a marked advantage due to the high capacity per unit weight.

The actual process has proved itself reliable and easy to operate over a period of many months. It should be noted that the refrigeration unit employed in this machine is a small commercial unit operating under ordinary temperatures and is not to be confused with the huge refrigeration system employed in the direct cold surface condensation methods where operation must be conducted in the difficult sub-zero region.

Experiments now in progress indicate another advantage of controlled adsorption for desiccation. The great capacity to take up water vapor rapidly, permits the application of relatively large quantities of heat to the ampoules without melting the contained material. This drives off the vapor more rapidly and greatly shortens the desiccation time. Also important is the margin of safety that this capacity gives under normal operating conditions when substances such as virus preparations are to be desiccated, since evaporation will continue with such speed that the temperature will remain well below freezing until the desiccation is essentially complete.

This is a point of greatest importance, if overloading and thawing or even near thawing is to be avoided. Proper attention to these considerations

\* Note: For large capacity machines this two-stage operation can be used routinely, by employing two desiccant chambers. These are both connected to the manifold by electrically operated remote control valves contained within the large tube uniting the two chambers. Such a valve presents no difficulty because of the slight difference in absolute pressure in the two chambers.

valve so that the direction of flow is always away from sterile area to non-sterile. When degassing is sufficiently complete the valve (4) is kept closed and when the vacuum, as measured by a special gauge<sup>12</sup> goes to about 1500 (absolute pressure in microns) snap freezing occurs spontaneously as a re-

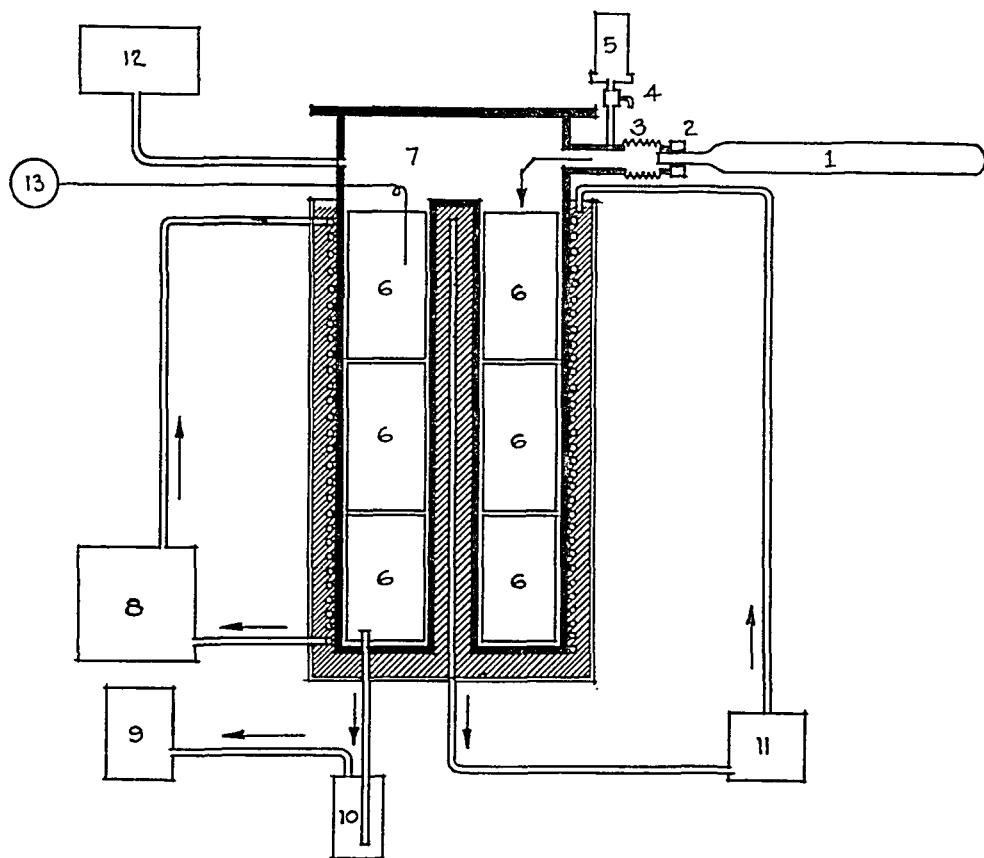


FIG. 1. Diagrammatic sketch of equipment.

sult of the rapid evaporation. Prior to freezing the ampoule is raised to a horizontal position to present a maximum evaporating surface. Evaporation (more correctly sublimation) continues from the frozen surface until the serum has reached the desired dryness.

In order to appreciate the advantages of controlled adsorption in our process it is necessary to understand the problem of water vapor removal. This apparently simple problem has presented most of the difficulties in all prior methods of desiccation.

In order to freeze and maintain the substance being processed in the frozen state, a sufficiently low vacuum must be held in the system. A vacuum pump is used to remove the non-condensable gases (air), from the system. Evaporation of water is accelerated as the pressure is reduced and in a relatively short time as the pump continues to remove the air, the system will be almost entirely filled with water vapor with continually diminishing

poules. For current routine use, the plasma is redissolved in pyrogen free water to make a four times concentration, placed in small Erlenmeyer flasks, and kept frozen at  $-18^{\circ}$  C. For use this plasma is melted in a  $37.5^{\circ}$  C. water bath and given with a large syringe (100 c.c.).

### INDICATIONS AND CLINICAL RESULTS

The plasma has been given in concentrated form (1) to replenish deficiencies in blood protein, (2) to build up or sustain blood volume, (3) for hypertonic effect in reducing edema, and (4) in a miscellaneous group. When hypertonic effects were not desired or if additional fluid was needed, a suitable amount of saline was given after the administration of the concentrated plasma.

To date 66 doses of concentrated plasma have been given intravenously to 45 individuals. In this series no definite febrile reactions were encountered in any instance. In fact, examination of charts of these patients shows that febrile patients have as a rule exhibited a substantial drop in temperature of 1 to  $1\frac{1}{2}^{\circ}$  F. depending somewhat upon the height of the fever. As a rule the plasma was given over a period of 10 to 15 minutes, but on some occasions, particularly in emergency, such as in severe shock, the entire dose has been given as quickly as  $1\frac{1}{2}$  minutes. The largest dose given at one time was 170 c.c. This would be equivalent in protein content to 1360 c.c. of whole blood. This is in accord with the practice of not exceeding 200 c.c. for a single dose to adults.

A detailed analysis of clinical results will be reported later when a larger, more complete series of cases has been compiled. However, even in this small series fairly obvious and definite advantages in the use of concentrated whole plasma stand out. The best results were obtained where there was local edema combined with reduced blood volume in shock. This was to be expected since concentrated plasma builds up blood volume by withdrawing water from the tissues. Such cases as shock with head injuries have responded favorably.

In shock from acute hemorrhage (ruptured ectopic pregnancy) concentrated plasma has rapidly built up the blood pressure prior to transfusion and operation.

In a small series of burns, several very severe cases have responded to the use of concentrated plasma with the relief of shock and apparently accelerated healing with maintenance of blood protein levels. The plasma was given with or without additional fluid according to the patient's fluid balance. Concentrated plasma alone was employed to advantage when the patient was "water logged" from prior administration of large amounts of saline.

Blood protein levels have been successfully maintained by the intravenous administration of concentrated plasma in several cases where adequate diet could not be taken by mouth. These patients all showed improvement with increase in strength.

Lednum<sup>18</sup> the mechanism by which this surface adsorption takes place is not actually known as the effects are beyond the powers of the most powerful microscope but a careful study by numerous investigators indicates the probable combination of three separate effects.

The first of these is probably the formation of a layer of the adsorbed

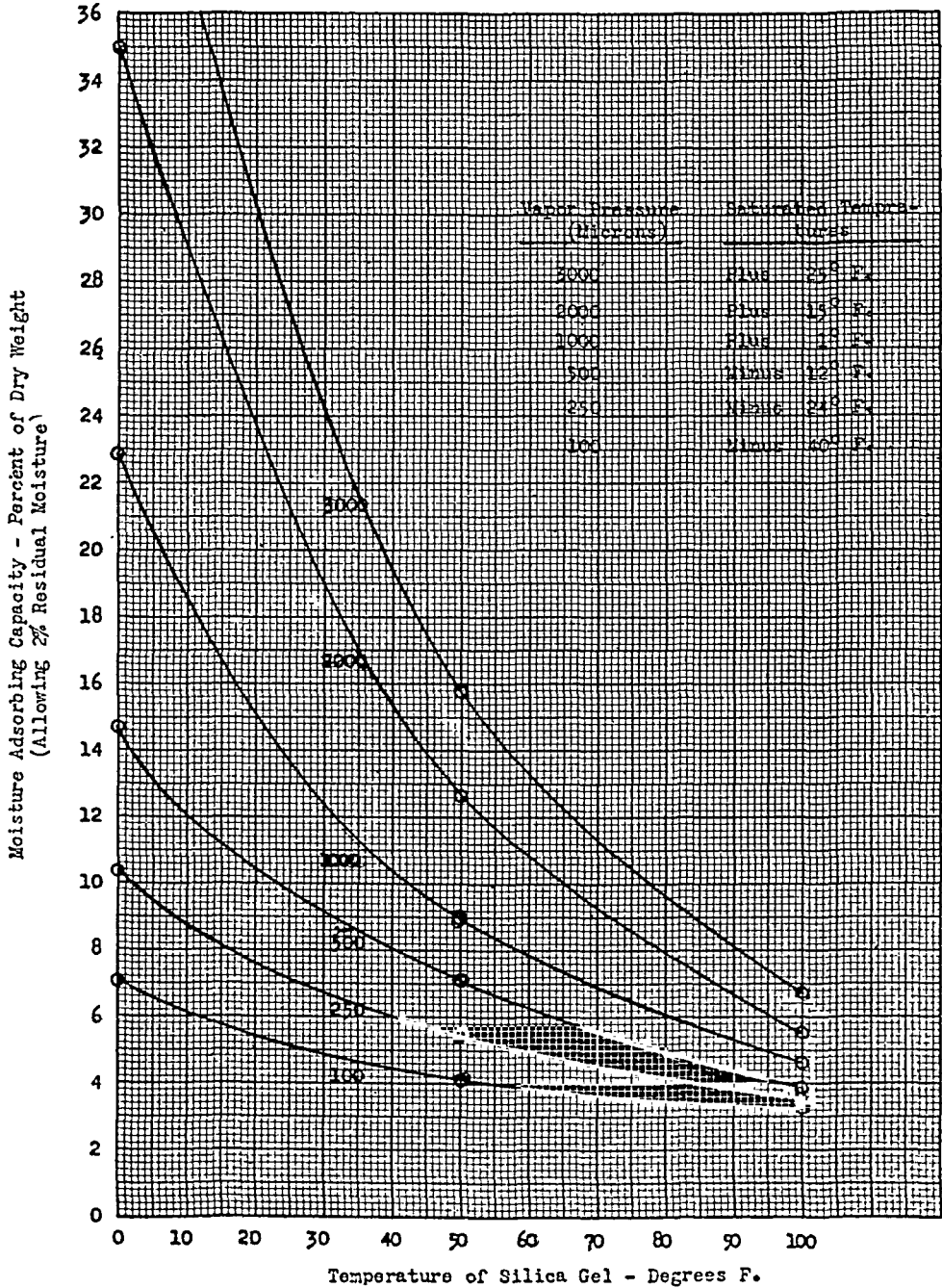


FIG. 2. Capacity-temperature relation of silica gel at vapor pressure (microns) as indicated on curves. Curve No. 2.

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For the desiccation of large quantities of ordinary plasma we have used ampoules of great capacity, usually 500 c.c. We have not observed the restrictions laid down by Flosdorf and Mudd<sup>6</sup> in respect to ratio of fluid volume to surface. On freezing, stratification occurs with great increase of surface with satisfactory rapid drying. The size of the ampoule neck has been kept as large as possible to keep restriction of vapor flow to a minimum. The use of metal bellows for flexible coupling has also eliminated the constriction which rubber tubing always imposes. With 200 c.c. quantities per ampoule satisfactory drying of plasma has been accomplished in six hours.

Figure 3 is a photograph of the machine now in use.

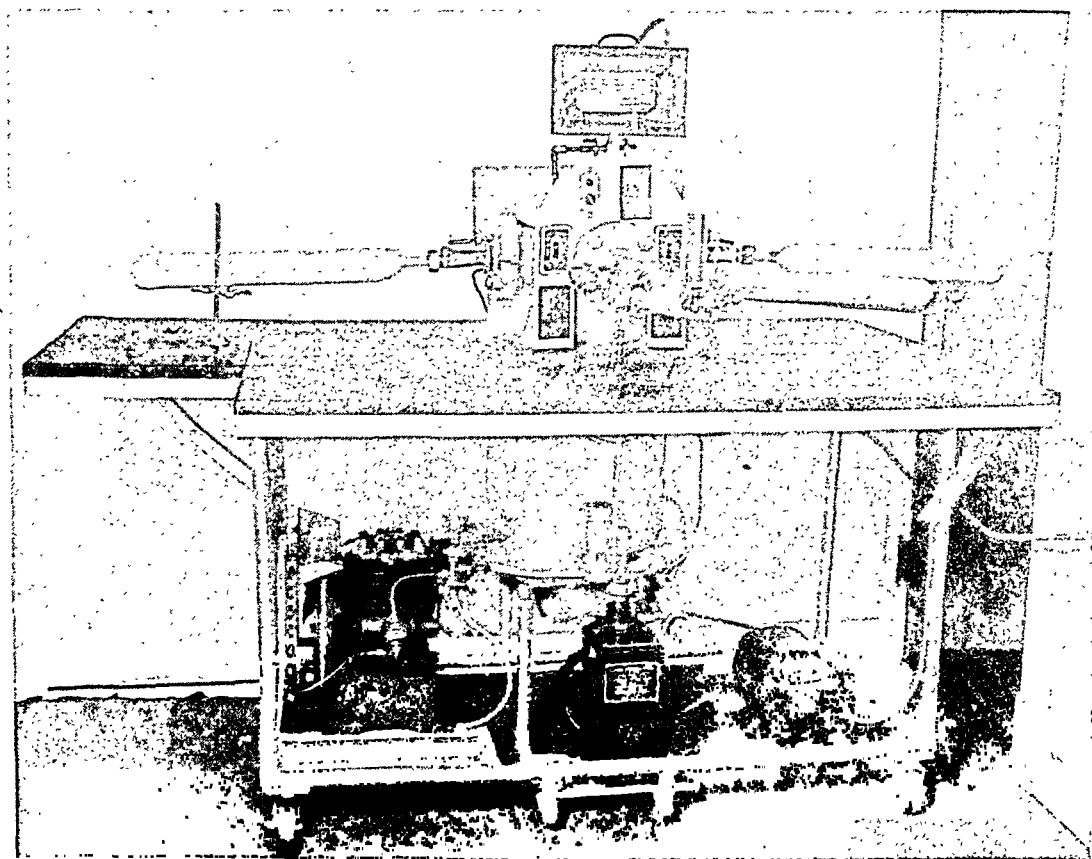


FIG. 3.

### DISCUSSION

In comparing our process with prior methods we have considered the following points: quality of product, economy of operation, practical maximum capacity, reliability, ease of operation, and initial cost.

The quality of materials can be estimated most satisfactorily by extensive use. Our clinical results from the intravenous administration of plasma desiccated by this process are briefly summarized in a later section of this



cred in the preparation of a pure extract is that smut does not grow readily on artificial media, and that the culturing of rust is impossible.

A brief description of the mode of occurrence of rust and smut in nature is necessary in order to understand its effect on asthma.

### SMUT

Smut fungi occur on a wide range of hosts, the most common ones being the cereals and grasses. In this part of the country the most important species are the stinking smuts of wheat (*Tilletia tritici* and *levis*), the smut of corn (*Ustilago zeae*), and that of oat (*Ustilago levis*). Smut spores infest the plant of the grain by attacking its fruit where they develop black, dusty masses. In some grains, for instance in corn, they produce tumor-like formations of considerable size which usually replace the tassels and the ear of corn in its entirety. When the fungus has used up all the tissue of the affected organ as food material, the whole diseased structure represents a mass of hyphae which produce millions of black spores called chlamydospores. At harvesting time these spores separate from the hyphae, are scattered by the wind for many miles, and settle upon old corn stalks, soil, or manure, where germination takes place the following spring. A large part of the spores may remain alive for four to five years, especially under the influence of moisture. When the new spores begin to bud they produce another type of spores called basidiospores. These are readily carried by the wind when the seed germinates, and infest the young seedlings of grain. They grow up with the stem of the grain and attack the young kernels by feeding upon their substance.

The smut spores which we observed on our slides in midsummer are the chlamydospores. They are round, brownish-black bodies, variously sculptured, showing small spicules on their surface similar to those of ragweed pollen. Most smut spores are considerably smaller in size than ragweed pollen, having a diameter of 5 to 9 microns. Some smuts are difficult to cultivate even if the grain of their host is used as culture material. The spreading of the spores and the breaking up of smut balls are greatly aided by the threshing of the grain. During this time the air becomes more intensely filled with the spores.

### RUST

The growth of rusts is more complex than that of smuts since rust requires two hosts for the completion of its life cycle. Rust spores infest the stems, not the fruit, of the various grains, grasses, and fruit trees. We have been particularly concerned with grain rusts (*Puccinia graminis*), especially those of wheat and barley. We are also studying rusts of grasses, especially of timothy and blue grass.

The spring stages of the wheat rust occur upon the leaves of the common barberry bush, the summer and winter stages on the stems of the wheat plant.

would probably eliminate the need for cumbersome and expensive external refrigeration of the containers or ampoules.

Estimates of the initial cost of the machine are not as yet complete, but it is apparent that on a capacity basis it should be considerably less than machines now available.

#### SOURCE OF PLASMA SUPPLY

The Blood Bank constitutes an ideal organization to obtain an adequate supply of plasma. Donors are required to give an amount of blood sufficient to produce the amount of plasma given. For example since blood is about one-half plasma and since a four times concentration is effected, it would theoretically require eight times the volume of blood to produce the maximum concentration of serum. Since some plasma is lost in separation from cells, and in filtration, a 10 to 1 ratio is more nearly correct.

Blood given for the purpose of replacing plasma is ordinarily kept in the Blood Bank up to the maximum of 10 days. This is of value to the Blood Bank in keeping an adequate supply of all types of whole blood available. Conversely, the Blood Bank is of assistance to the plasma department since all blood from the bank when outdated at the tenth day is processed and stored.

In preparing the plasma a technic similar to that of Mudd, Flosdorf, Eagle, Stokes and McGuiness<sup>9</sup> was used at first. More recently a new technic, eliminating the restrictions imposed by the type specific agglutinins has been adopted as routine. The removal of agglutinins is accomplished by adsorption on red cells as a result of pooling the different types of whole blood and immediately separating the plasma.

Accompanying hemolysis is kept at a minimum by working rapidly at low temperature. Hemolysis is also retarded by the low complement content of 10 day old blood. However, some hemolysis has occurred with definite coloring of the plasma. An approximate determination by the New-comer method using a one to four dilution has shown a maximum of 0.3 grams per 100 c.c. of plasma. The agglutinin titer has varied from 0 to 1:1.

Since we have observed no evidence whatever that hemolysis causes reactions in six months' experience with blood banking we did not hesitate to use plasma containing small amounts of hemoglobin. This is contrary to the commonly accepted opinion in blood banking. However, no febrile or other type of reaction (with the exception of two transient urticarial manifestations) has been observed in the use of such plasma in concentrated form.

Following a suggestion of Levinson,<sup>10</sup> we have omitted filtration of plasma after desiccation and reconstitution as a liquid. Clinical results have been unchanged, and loss of valuable concentrated plasma in the filter is thus eliminated. Seitz filtration of plasma separated from pooled blood is performed prior to processing.

Plasma intended for long storage is vacuum sealed in the original am-

than that of timothy, but not as high as that of the ragweed curve. Alternaria was present throughout the time of observation and continued late into the fall. Other investigators have stressed the importance of alternaria as a cause of seasonal asthma, particularly in July and August. The alternaria curve shows a more or less generalized distribution of the spores throughout the whole time of observation with relatively little variation and only a few discernible peaks.<sup>2</sup> In our experience with pollen<sup>9</sup> we noted that

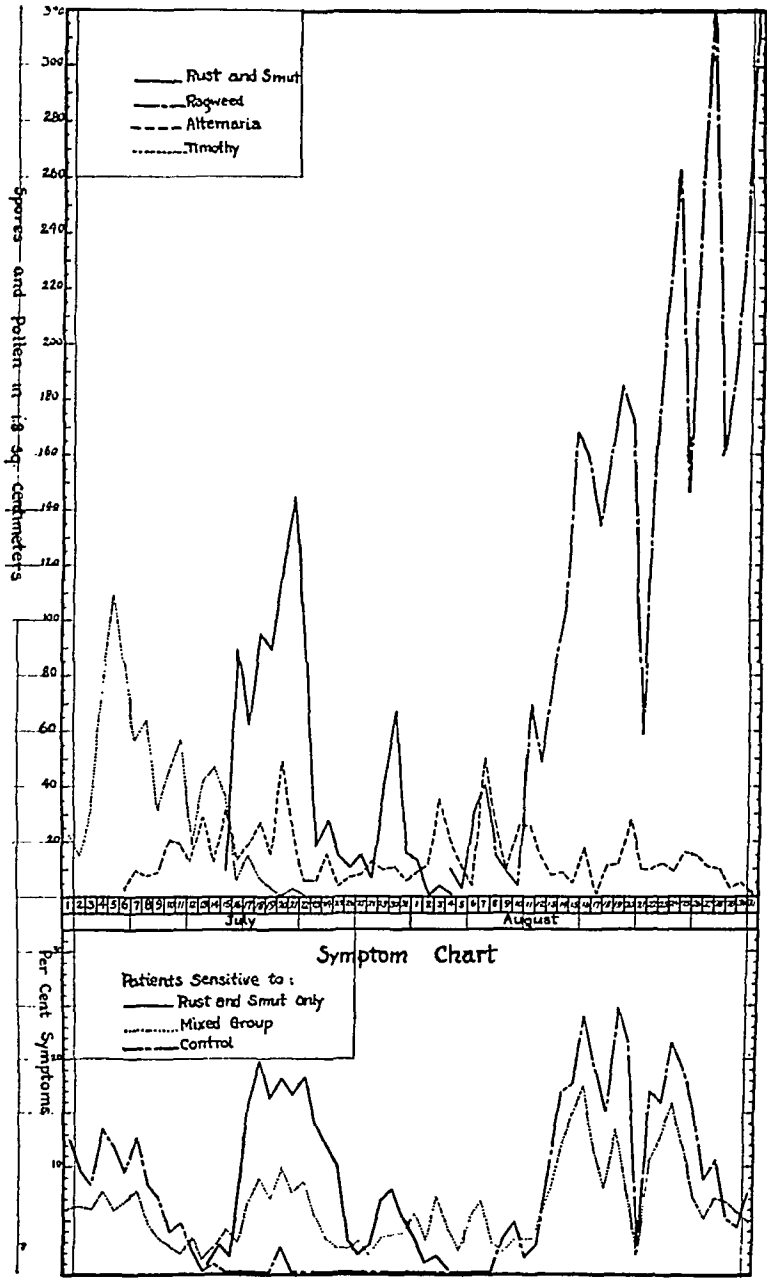


FIG. 1. Daily rust and smut count compared with counts of ragweed, timothy, and alternaria. The symptoms chart below shows the summation of the daily "symptom marks" for each group of patients.

Convalescent sera have also been dried, stored and used with good results. Obviously time has not permitted the determination of the effect of prolonged storage.

The process has been entirely satisfactory for laboratory uses such as preservation and concentration of typing sera, preservation of cultures, positive sera, and thromboplastin extracts for the prothrombin test.

### CONCLUSIONS

1. A new and improved process for the desiccation of plasma, serum and biological substances from the frozen state is reported.
2. The thermodynamics of this type of desiccation are investigated and discussed.
3. The operation of this process in connection with a Blood Bank to assure an adequate supply of plasma for routine intravenous use is described.
4. A preliminary report of clinical results in a variety of conditions is given.
5. No febrile or other harmful reactions were noted in 66 successive intravenous administrations of concentrated plasma to 45 cases.

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cated because of the possibility that, with our mode of preparation of the rust, skin reactions to straw could have been encountered.

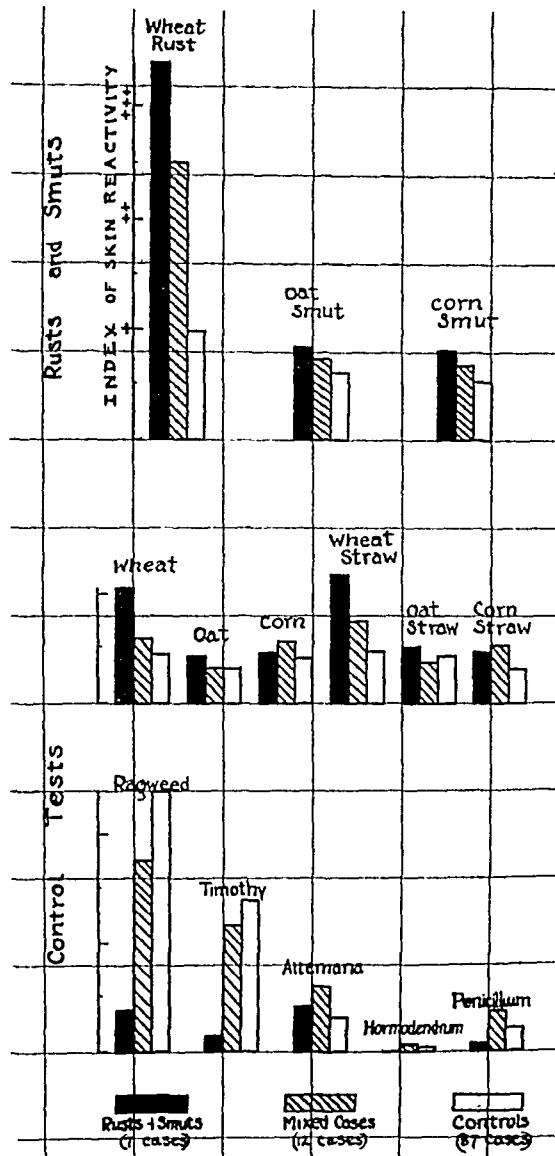


FIG. 2. Average size of skin reactions for wheat smuts, oat and corn rusts in the three groups of patients, compared with the skin reactions of the control antigens.

## RESULTS

Figure 2 records the averages of the intradermal skin reactions which had been graded from one to four plus in the three groups of cases under consideration, namely, in those patients who had symptoms exclusively during the rust and smut season (seven), those who suffered definite exacerbations at the time (12), and the control group of 87 cases without manifestations at the season in question.

## RUST AND SMUT, MAJOR CAUSES OF RESPIRATORY ALLERGY \*

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*Detroit, Michigan*

DURING the past few years we have observed that a certain number of patients manifested unusually severe asthmatic symptoms during the month of July and during the early part of August. We attributed this at first to such pollens as the plantains and lambsquarter, and to a residual effect of the timothy pollen. However, by thoroughly checking the symptoms against the daily pollen counts, by frequently retesting for the then prevailing pollens, and by administering what we felt was adequate treatment to those patients who exhibited more or less pronounced reactions to these pollens, we were unable to establish such an etiological correlation.

Another source of asthma during that period was suggested by the studies of Feinberg<sup>1</sup> on molds. In pursuance of his work we carried out a local survey during the past year in collaboration with Ackley.<sup>2</sup> The data obtained from this survey warrant the conclusion that those fungi which Feinberg named as the most probable causes of asthma, namely *alternaria* and *hormodendrum*, did not play the major rôle in causing the symptoms in our patients. The following evidence shows, instead that spores of smut and rust in the air were instrumental in causing allergic symptoms of the respiratory tract during that period of time.

The literature includes three cases of asthma reported by Cadham<sup>3</sup> in 1924 in which wheat rust was believed to be the cause. In his report, however, Cadham presents definite confirmation of the clinical impression by skin tests. Another more recent paper by Wittich and Stackman<sup>4</sup> relates the case of an individual working in a milling district whose asthma was caused by corn smut. This paper is illustrated by a photomicrograph of smut present in the stained sputum. Wittich<sup>5</sup> has recently observed 11 asthmatic patients in whom smut sensitivity appeared to be the major cause. Duke and Durham<sup>6</sup> were first to mention the appearance of rust and smut spores on exposed slides. They found that in Kansas City during May, June, and July, 1927, rust spores were more numerous than all other types of pollen grains. Durham<sup>7</sup> noted in his recent survey on fungi that spores of smut and rust appear very frequently. Brown<sup>8</sup> considered grain rust (*Puccinia graminis*) of sufficient importance to include it in his routine skin testing for molds.

In an investigation of this subject, one of the chief difficulties encount-

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This investigation was made possible by a grant of Mr. J. E. Fields, Detroit, Michigan, which is gratefully acknowledged.

There was a positive familial history of allergy. The patient has had no other symptoms of allergy with the exception of "chronic sinusitis" about eight years ago which was promptly remedied upon removal of several polyps. He had had the usual childhood diseases, and pneumonia in 1935 and 1938.

The physical examination revealed nothing unusual, particularly with reference to the nasal passages and sinuses. Intradermal skin tests showed largely negative reactions, with exception of the tests to a few foods and to short and long ragweed and cocklebur. The latter reactions were two and three plus. Not having any other clue for treatment at the time, we gave the patient weekly injections for these pollens. About July 5 the nose became markedly congested, and within the following days a typical state of asthma developed which was particularly pronounced at night.

On July 8 intradermal tests for fungi, following scratch tests, revealed four plus reactions to rust, two plus reactions to smut, and a two plus reaction to monilia. Within 10 minutes after the injections a generalized reaction occurred which appeared to have its origin at the site of the rust injection. This was promptly controlled by 0.2 c.c. of epinephrin. The asthmatic condition, as well as the nasal symptoms, subsided promptly for about three days. During the following days treatment with a 1:100,000 dilution of rust extract was given which completely relieved the patient. On December 18 a small amount of rust powder was blown into the air close to the patient's nose. A violent attack of sneezing, followed by asthmatic wheezing, was precipitated within a few minutes. Administration of 0.5 c.c. of epinephrin promptly controlled the attack.

Case 2. F. K., a four year old boy, was first seen on July 11, 1937, because of asthma which had been present practically throughout the year for two consecutive years, with definite aggravations about July and August. He also presented evidence of pronounced allergic eczema on hands, face, and neck, which had first appeared when he was six months old. Various members in both parental families were reported to be allergic. When the patient was first seen the symptoms of rather severe asthma were present and a large number of positive skin reactions was obtained, particularly to wheat, milk, egg, several trees, and grasses. An eliminative régime, as well as hyposensitization against the most important reactors, resulted in improvement of the eczema. The asthma, however, did not subside until the first part of September. During the winter months of 1937-1938 the boy was entirely free from asthma and suffered only from occasional upper respiratory catarrhs.

In March 1938 retesting with most of the previously reacting antigens showed no essential change. The test for wheat rust and corn smut was four plus, and that of oat rust, two plus. Among other fungi, hormodendrum, penicillium, and monilia gave one to two plus reactions. Hyposensitization with 26 injections of wheat rust extract was initiated with a 1:1000 dilution, which resulted in very strong local reactions at the site of injection. During 1938 only one asthmatic attack occurred, on July 18, which we felt was due to the combined effect of the rust spores in the air and a rather large dose of the rust extract administered that day. Otherwise the boy has been entirely free from trouble. On January 6, 1939, the boy was subjected to inhalation of dried alternaria powder which caused no irritation whatsoever. When the powder of rust was blown toward his nose violent sneezing, followed by some wheezing, ensued, from which the boy recovered spontaneously within 15 minutes.

#### COMMENT

It is true that in a given case it is often difficult to evaluate the importance of a certain antigen as the cause of allergic manifestations on the basis of clinical evidence. However, when the cases are as numerous as those re-

*Barberry Stage:* In early spring two types of "yellow pustules" appear on the barberry leaves. They can first be seen on the upper surface; and shortly after larger sized pustules appear on the lower surface. These pustules are made up of numerous small, cup-like structures called aecia. When these cups break open they discharge masses of yellow spores called aeciospores, which are scattered by the wind.

*Grain Stage:* The aeciospores fall upon the young stems of grains, produce elongated yellow streaks underneath the epidermis of the stems and the leaf sheaths of the grain. This first visible evidence of rust on cereals is called uredinia or red rust. With further growth the lesions push outward and finally break through the surface, thus exposing a reddish brown mass of spores (urediniospores). They are stalked, one-celled, and ovate in form. Each spore contains two nuclei, is rather thick-walled, and bears numerous small, spiny projections. Under the influence of moist, warm weather they may produce successive growths of their own kind about every seven to 10 days throughout the growing season. These spores are disseminated by the wind; they were found on our slides throughout June and July. Durham states that in large grain centers of the United States, the concentration of wheat rust in the air may reach 980,000 spores per cubic yard.

Usually in late summer and fall, black pustules or telia, containing teliospores, appear on the same culm and leaves. These pustules are dark-colored, stalked, bicellular, with a diploid nucleus, spindle-shaped, and thick-walled. Unlike its predecessor, however, the teliospore cannot germinate immediately, but must pass through a dormant period, wintering on the stubble or on the ground until early spring. Then the black pustules send out small, thin-walled, short-lived spores called basidia which are carried by the wind to the barberry leaves. There they start the life cycle anew.

#### SPORE COUNT

Since July, 1938, we have charted the number of rust and smut spores found on the vaseline-coated slides which were exposed for 24-hour periods for our routine pollen counts. Figure 1 presents the daily number of the rust and smut spores counted on 1.8 square centimeters of the exposed slides. This curve is compared with that of alternaria, which is the most easily recognizable fungus spore in season at that time, and with the curve of the two most important pollens then encountered, namely timothy and ragweed. Because of the difficulty in differentiating definitely between the rust and smut spores on the slides, we did not attempt to present separate curves for each. The first urediniospores of rust occurred about July 15 and reached a rather high peak about July 21, on which day 149 spores were counted. The peak on July 30 is probably attributable chiefly to smut, but there was still a small number of rust spores on the slides during the early part of August. In comparing this curve with those of timothy and ragweed pollen, and that of alternaria spores, we find that the peaks of the rust and smut curve are higher



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the severity of symptoms of hayfever and asthma does not depend as much on the quantity of a certain pollen in the air as on the rapidity of the increase and decrease in its concentration. If this observation can be accepted in the interpretation of the fungus spore curve, we would expect to encounter more symptoms from sensitization to rust and smut than to alternaria because of the different character of the curves.

#### METHOD

Our clinical observations are concerned with the summer stage of rust, namely the urediniospores, and the chlamydospores of smut which were present on our slides at the time in question. Extracts were prepared from the pustules of red rust of wheat and oats and the smuts of oats, barley, and corn. The mechanically separated fungus material was killed by exposure to 5 per cent thymol in concentrated alcohol. This was evaporated, and the residue was extracted in saline solution and passed through a Seitz filter.

Our survey was carried out on 106 consecutive patients with asthma and nasal allergy. Among these, seven asthmatics exhibited symptoms at no other time than late July and early August. In a second group of 12 patients, 10 suffered more or less severe exacerbations of a perennial asthma during that time, and two suffered similar exacerbations of nasal catarrh. The other 87 cases exhibited no symptoms at the time in question.

The adequacy of this arbitrary division of our cases into three groups was well illustrated by a study which had been carried out for another purpose. Throughout the summer months of 1938 most of our patients had been instructed to keep a very close record of the dates of their symptoms. In their daily symptom chart the severity was graded one to four plus. We were able to utilize the records of all the patients of groups one and two, and 48 of those of group three. The second portion of figure 1, marked "symptom chart," represents a summation of the plus marks on these records. A definite parallelism of the "symptom curves" with the fungus curves is noticeable in the first and second groups, a fact which is highly suggestive of an etiological connection of the symptoms of these patients with the rust and smut.

Scratch and intradermal skin tests were performed for the rusts of wheat and the smuts of corn and oats. As control tests we applied extracts from the grains, as well as of the straws of the selected rusts and smuts, namely of wheat, oats, and corn. Furthermore, we tested all of the 106 patients for alternaria, hormodendrum, and penicillium, as well as for timothy and ragweed, since these pollen and fungi were constantly present in the air during the season in question. The straws of wheat, corn, and oats which were used for extraction had been examined microscopically and were found to be free of rust and smut infection. We felt that this latter control was indi-

skin tumor of mushroom-like consistency measuring about 4 centimeters in diameter. Overlying the left elbow was a small subcutaneous nodule measuring one centimeter in diameter, freely movable and non-tender. The right mandible was considerably larger than the left; the soft tissues of the cheek and right submaxillary region, and the mucous membrane overlying the right lower alveolar process and the right side of the floor of the mouth were hypertrophied to a moderate degree (figure 2).



FIG. 1. Photograph of patient showing multiple café-au-lait spots, particularly over lower abdomen and upper thighs.

The three groups, which were arbitrarily established by the history of their symptoms, showed also a distinctly different response to skin testing which conformed well with our clinical impression. The seven patients with symptoms only in July and early August exhibited by far the strongest reactions to the rust and smuts, whereas their reactions to pollen and the other fungi were considerably less pronounced. The 12 patients suffering exacerbations at the rust and smut season reacted less to rust and smut, but gave stronger reactions to the pollens and the other fungi. In the control group the reactions to rust and smut were negligible, but those to pollens were most pronounced. The smut and rust sensitive patients were also more sensitive to the respective cereals and their straws than were the other patients. In no case, however, was the individual reaction to the grain as strong as that to the fungus.

The total group of patients gave only minor skin reactions to the other fungi tested, such as penicillium and hormodendrum. This may or may not indicate a relative lack of significance of these molds in a consecutive number of allergic patients in this part of the country as compared with rust and smuts.

#### CLINICAL OBSERVATIONS

During this study we encountered two patients in whom the intradermal skin tests for rusts produced generalized reactions, even though the usual precautions of a preliminary scratch test were carried out. Hyposensitization with rust and smut extracts was attempted in all of the suspected cases. In some the effect was very striking, the symptoms subsiding after two or three injections. The evaluation of the effect of this treatment, however, is difficult because of the relatively short duration of the fungus season, which may have accounted for spontaneous recovery in some of the patients.

There are many different types of rusts and smuts as pointed out above. Unfortunately, we were unable to carry out extensive cross testing with the various species. The majority of the patients with positive reactions to rusts also reacted positively to smuts, but the reactions to smut were not as frequent and as pronounced as those to rust. The serum of two patients with strongly positive intradermal responses to rust produced positive passive transfer reactions on normal individuals. The following two cases, namely, patients who had symptoms at this season only, and those who suffered aggravation of symptoms during the season in question, are reported because they are typical of the two first groups. In both cases asthmatic symptoms were reproduced upon inhalation of rust powder outside of the season.

#### CASE REPORTS

*Case 1.* R. D. C., a 20 year old male, consulted us on March 7, 1938, because of symptoms of "hay-fever" and a severe cough, which had occurred during July and August for the past three years. During the balance of the year, and especially during the ragweed season, the patient stated that he had been free from symptoms.

The general structure was characteristic of neurofibroma. Biopsy of the jaw, performed through the oral surface on January 8, 1938, revealed similar histological characteristics (figure 4).



FIG. 3. Roentgenogram of right mandible showing cystic loculation and marked destruction of major part of ramus.

Extensive surgery for the jaw condition was thought to be contraindicated because of the benign nature of the lesion, the high incidence of local recurrence and the possibility of malignant metaplasia following surgery in these cases. Radiotherapy was not advised since these lesions are usually extremely radioresistant.

*Case 2.* R. G. was first brought to the Mandel Clinic of the Michael Reese Hospital on January 11, 1935, at the age of two, because of a progressive enlargement

corded here we feel justified in assuming that rust and smut play a prominent part as a source of asthma and upper respiratory allergy. The following reasons emphasize this point:

1. The spores of rust and smut are small in size and spiculated, making them more buoyant. In contact with respiratory mucous membranes they are likely to produce more irritation than antigens with a smooth surface.

2. The mode of appearance of the spores in the air, as indicated by the spore curve, is particularly apt to induce symptoms. Their periodic appearance in midsummer, their absence during a large part of the year, the relative suddenness of the spore concentration in the air, and the rather high peak, are factors which in our experience with pollen have been found to render the antigen more harmful to patients.

3. The frequency of obtaining positive skin reactions in a routine series of patients with respiratory allergy is rather striking. Cases with symptoms of respiratory allergy during the rust and smut season showed the strongest positive reactions to rust and smut.

The marked antigenicity of the material is well demonstrated by the size of the wheals produced by the scratch and intradermal skin tests; by the occurrence of generalized reactions, and by the prompt reproduction of symptoms following inhalation of the spore powder.

In a recent communication Wittich<sup>5</sup> noted a marked prevalence of smut spores in Minneapolis in the latter part of the fall. He found that they originate in the vast grain storing centers of the Minneapolis district. In Detroit the exposed slides did not reveal smut spores at this late season.

#### SUMMARY

1. A daily slide survey was made for spores of rust and smut. The curve exceeded in height the peak of the timothy curve and reached its maximum about July 23 and 30. The spore curve did not reach the height of the ragweed curve.

2. Among 106 consecutive cases of asthma and upper respiratory allergy, seven had symptoms exclusively at the rust and smut season, and 12 patients showed more or less severe exacerbations at that time.

3. The average intradermal skin reactions for rust and smut in these patients were compared graphically with reactions to other important antigens. Considerably stronger reactions to rust and smut occurred in the first two groups of patients, who exhibited symptoms at the time in question only.

4. In the two cases here reported an attempt was made to reproduce asthmatic attacks by inhalation of rust; this was accomplished without difficulties.

5. On the basis of the above findings, we consider sensitivity to rust and smut an important cause of seasonal allergy of the upper respiratory tract.

of cutting through neurofibromatous tissue. Consequently, radiotherapy was administered to the left upper and lower tibial epiphyses on the 4 gram radium pack in the attempt to delay the growth of the leg. The radiation was distributed over a period of two years, five cycles being given for a total of 60,000 milligram-hours to the lower



FIG. 5. Photograph of mother of our second patient showing generalized neurofibromatosis and pachydermatocoele over right supragluteal region.

tibial epiphysis and 30,000 milligram-hours to the upper. Lateral and medial portals of entry, each measuring 6 by 8 centimeters, were employed at each epiphyseal zone. The skin-target distance was 10 centimeters; the filtration was 1 millimeter of platinum.

# VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS WITH BONE MANIFESTATIONS\*

By ERICH UHLMANN, M.D., and ABRAHAM GROSSMAN, M.D.,  
*Chicago, Illinois*

THERE has been profound change in our conception of the disease originally described by von Recklinghausen in 1882 in his article on "Fibrome der Haut." For many years the disease was looked upon as a disorder of the peripheral nerves alone, especially of the cutaneous filaments. Multiple soft nodules of the skin (*molluscum fibrosum*) and the subcutaneous neurofibromata so frequently associated with them were considered the main attributes of the clinical condition. By 1901 Adrian had collected 407 cases, in many of which pigmentary changes had either anteceded or were coexistent with the formation of neurofibromata. The recognition of allied pigmentary disturbance raised some doubt as to the ectodermal nature of the disease. This was again questioned by Weiss, who in 1921 noted and commented on the scoliosis observed in 15 cases of von Recklinghausen's neurofibromatosis and suggested that bone changes would be found with increasing frequency in this disease. The classical paper of Brooks and Lehmann (1924) left no doubt as to the importance of bone changes in this condition and stamped it as a bizarre disease of protean manifestation rather than the simple cutaneous and subcutaneous neurofibromatosis described by von Recklinghausen.

The recent observation of two patients with von Recklinghausen's neurofibromatosis accompanied by unusual osseous changes prompts us to add these to the literature and to review the condition briefly with particular attention to its bony manifestations.

## CASE REPORTS

*Case 1.* M. H., a 16 year old school girl, first presented herself for examination at the Mandel Clinic of the Michael Reese Hospital on September 7, 1937. She complained of an enlargement of the right jaw of which she had first become aware at the age of six and which had continued to increase in size producing a marked facial asymmetry. There was no familial history of any similar condition nor was the patient aware of the existence of skin tumors, pigmentation or epilepsy in any of her relatives. The patient's intelligence was apparently somewhat less than the average for her age (at 16 she was still in the first grade of high school).

Upon examination her entire body was found to be covered with multiple flat café-au-lait spots of varying size (from 3 millimeters to 15 millimeters in diameter) and of varying intensity of pigmentation. These pigmented areas were particularly numerous over the face, neck, trunk and abdomen; the pigmentation of the extremities was less marked (figure 1). In the right axilla was an umbilicated, non-pigmented

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From the Tumor Clinic of the Michael Reese Hospital, Chicago, Illinois.



margins. The fifth cervical vertebra showed a particularly marked degree of roughening, with bony proliferation in the form of a spur-like projection from the anterior edge of this vertebral body. By July 1938 a moderate torticollis had developed.

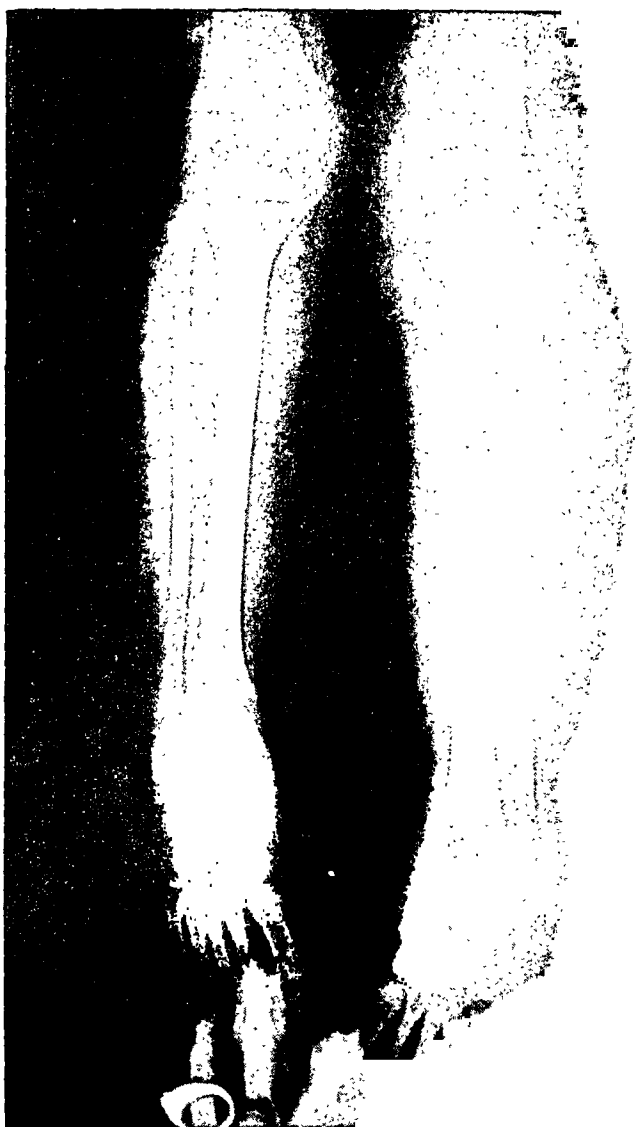


FIG. 7. Roentgenogram showing greater length of bones of left leg and diffuse neurofibromatosis of soft parts.

Radiation therapy was considered but thought inadvisable because of the radio-resistant nature of neurofibromata and since the lesions of the left leg had not responded to previous radiotherapy. Surgery was likewise thought to be contraindicated at this time because of the rapid recurrence of cervicothoracic neurofibromata following operation (Epstein) and the reports in the literature of sarcomatous change following incomplete surgery for cervicomediastinal neurofibromata (Hosoi).

Roentgenogram of the right mandible taken on September 11, 1937 (figure 3) showed the molar teeth impacted into one another; the ramus was practically replaced by cystic loculi occupying the width of the bone from cortex to cortex leaving very little recognizable bony trabecular structure. Roentgenograms of the skull and of both hands showed no pathological findings.



FIG. 2. Marked facial asymmetry due to enlargement of right mandible associated with von Recklinghausen's neurofibromatosis.

The blood Wassermann and Kahn tests were negative. The blood count was as follows: erythrocytes 4,660,000 with 80 per cent hemoglobin, leukocytes 10,200 with 74 per cent polymorphonuclear leukocytes and 26 per cent lymphocytes. The blood calcium was 11.8 mg. per 100 c.c., while the blood phosphorus was 4.5 mg. per 100 c.c. Urinalysis revealed no pathologic findings.

Histologic examination of the subcutaneous nodule overlying the left elbow revealed whorls of cells in parallel rows embedded in a moderately dense, fibrous connective tissue stroma. The individual cells were of spindle shape and of approximately the same size. The nuclei stained rather deeply and at times appeared vesicular.

malignant neoplastic disease, referred to the Tumor Clinic of the Michael Reese Hospital in the past six years there have been seven with generalized neurofibromatosis. One must recall that many patients with this disease are never referred to general hospitals or clinics for neoplastic diseases since



FIG. 9. Roentgenogram showing large cervical neurofibroma extending towards mediastinum and producing marked displacement of trachea.

there is so little to be offered therapeutically. The above figures, however, do suggest the relative infrequency of this condition.

According to Sharpe and Young there is no special geographic or racial distribution of the disease; it has been known to occur in the white, black, red and yellow races. Its incidence in the male is slightly higher than in the female. The condition has been observed in all age groups, the so-called *formes frustes*, characterized by pigmentation without tumor formation, being more common in infants and children.

There is undoubtedly a strong hereditary tendency associated with von Recklinghausen's neurofibromatosis. Preiser and Davenport, in a study of

of the left leg. When she was five months of age a few brown spots had appeared on the trunk and a more diffuse pale brown sheet-like pigmentation had been noted over the calf of her left leg. Shortly after this the left leg became heavier, fatter

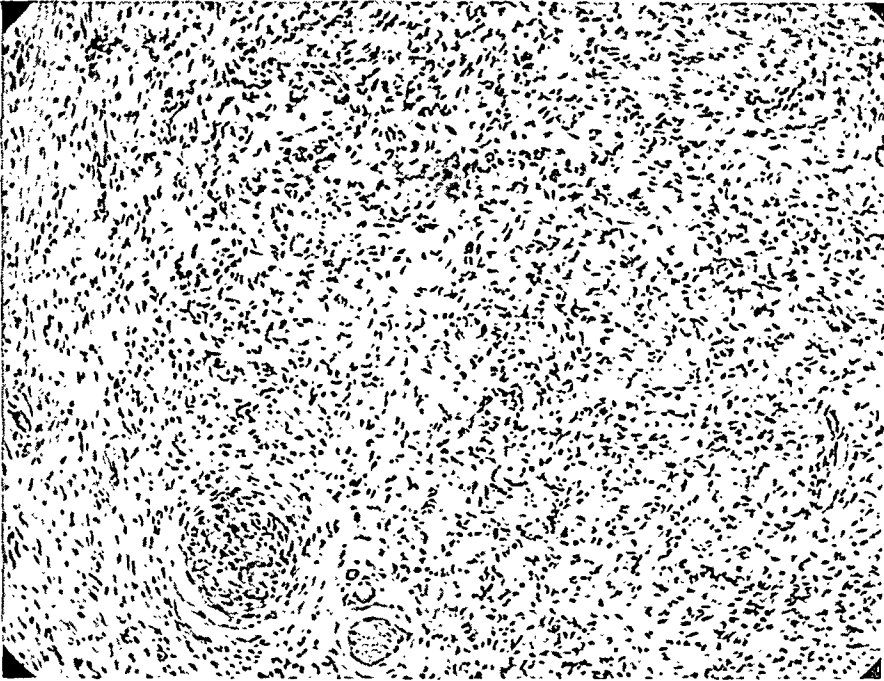


FIG. 4. Biopsy of right jaw. Magnification  $\times 80$ . Whorls of cells are seen arranged for the most part in parallel rows embedded in a moderately dense fibrous connective tissue stroma. An occasional nerve ending is seen. The histological structure is typical of neurofibroma.

and slightly longer than the right. Both the mother and grandmother of the patient had diffuse patchy pigmentation of the skin and multiple pedunculated skin tumors characteristic of neurofibromatosis. In addition, the mother of the patient had a pachydermatocele of moderate size in the right supragluteal region (figure 5).

Examination of the patient revealed numerous circular and oval café-au-lait spots from 1 millimeter to 1 centimeter in diameter on the trunk and lower extremities. The left leg was considerably larger than the right and was covered on its antero-lateral and posterior aspects from knee to ankle by a confluent café-au-lait pigmentation (figure 6). The entire left leg from knee to ankle presented a diffuse subcutaneous nodularity of rope-like consistency. Measurements in vivo and by roentgenogram (figure 7) indicated that the left tibia was about 2 centimeters longer than the right. In addition, the roentgenogram showed an increased density with diffuse mottling and nodularity of the soft tissues of the leg.

The blood Wassermann and Kahn tests were negative. The blood cell count revealed 4,300,000 erythrocytes with 70 per cent hemoglobin, and 9,950 leukocytes with 68 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes and 2 per cent eosinophiles. The urine test revealed no abnormal findings.

The condition was obviously that of von Recklinghausen's disease with gigantism of one leg associated with a marked neurofibromatosis of its soft tissues. Biopsy was thought to be contraindicated because of the risk of inducing malignant metaplasia thereby. Similarly, epiphyseal arrest by open operation, to check the accelerated disproportionate growth of the leg, was considered undesirable because of the danger

generations of one family, with a striking similarity of lesions, were observed. Five of the 13 patients exhibited osseous lesions which were mainly in the form of scoliosis and cystic changes of the skull.

A variety of congenital malformations have been reported in association with generalized neurofibromatosis. These include such conditions as cerebral meningocele, tuberous sclerosis, congenital glaucoma, spina bifida, defects and other anomalies of the fibula, ribs and other bones. In addition, imbecility and other mental defects, and psychogenic disturbances of many varieties have been observed in patients suffering from neurofibromatosis. Preiser and Davenport reported the existence of feeble-mindedness in 7.8 per cent of 243 cases of von Recklinghausen's disease.

Considerable controversy exists as to the etiology of this condition. The consensus of opinion is that it is an embryological derangement, particularly of the ectoderm. The coincidence of allied bone changes suggests mesoblastic involvement as well. A number of endocrine disturbances associated with neurofibromatosis have been described, and such glands as the pituitary, thyroid and adrenals have been suspected of bearing some physiological relation to this disease. These associated endocrine disturbances include such conditions as acromegaly, Fröhlich's syndrome, Addison's disease, myxedema, cretinism, delayed and incomplete sexual development. Because of the frequency of pigmentation in this disease the adrenal gland particularly has been suspected of bearing some significance in the development of von Recklinghausen's disease. It is to be remembered that any of the endocrine glands may be displaced or compressed by neurofibromata resulting in corresponding endocrinological syndromes.

The clinical course of this disease is subject to a wide range of variation. In most instances there are pigmentary changes consisting of grayish-brown café-au-lait macular spots and patches of various patterns, sizes, shades and numbers. Such pigmentation usually appears at birth or in early infancy, often preceding the formation of skin tumors. The lesions are especially numerous over the trunk and occasionally appear to be distributed in rather symmetrical pattern bilaterally. The face and extremities are sometimes spared but usually exhibit a few lesions. At times the pigmentation assumes a broad confluent sheet-like expanse. The individual zones of pigmentation are not distinguishable grossly from the ordinary benign pigmented melanotic naevi occurring on many individuals. The significant histological finding in sections through such pigmented zones is the presence of multiple thickened nerve endings in parallel club-like strands in the upper layers of the derma. These strands are highly cellular, the nuclei being somewhat spindle-shaped.

Occasionally, pigmentation occurs alone without tumor formation; such cases are known as *formes frustes*. Generally, however, the pigmentary change is the precursor of tumor formation. Such tumors may be limited to the skin and subcutaneous tissues or may involve any of the other organs of the body.

During each cycle the daily dosage varied from 500 milligram-hours to 1500 milligram-hours.

This quantity of radiation apparently had no effect on the subcutaneous neurofibromata nor did it retard the rate of growth of the leg. By November 20, 1937, the

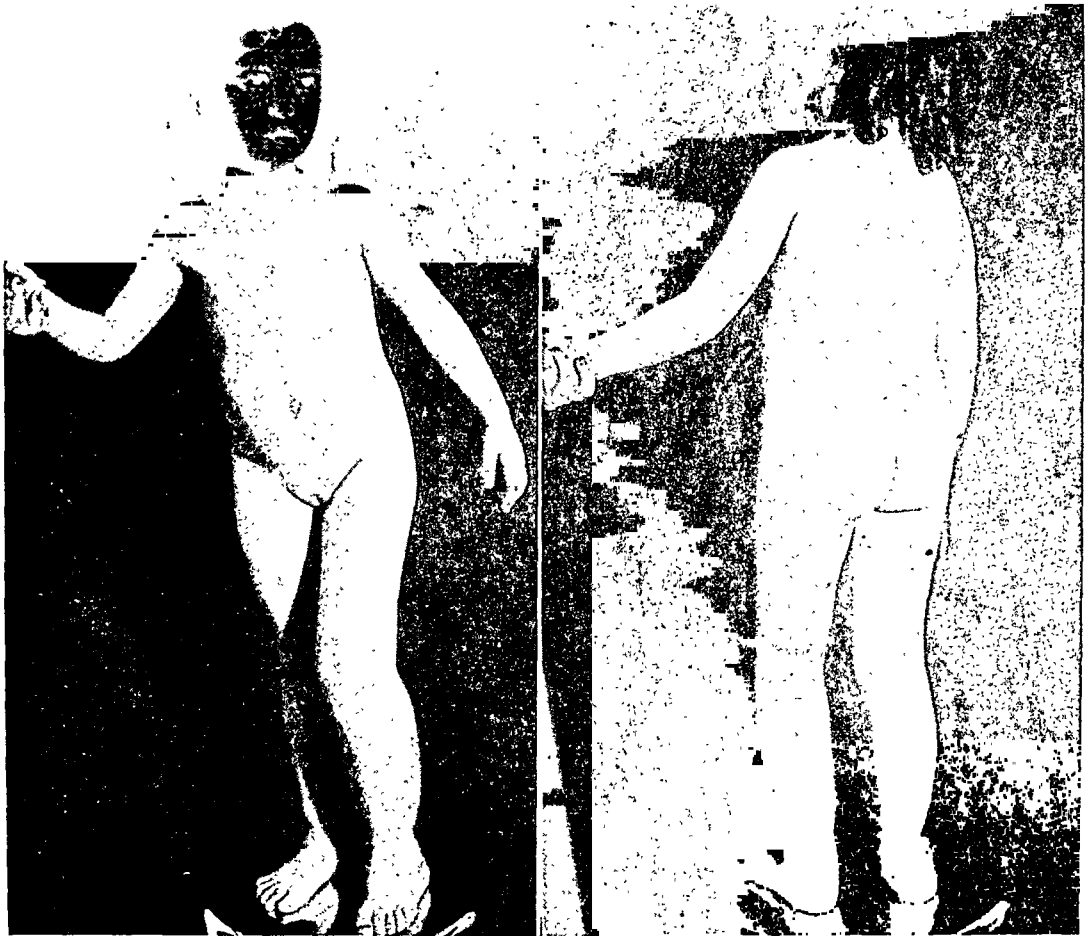


FIG. 6. Photograph of patient with diffuse café-au-lait pigmentation and hypertrophy of left leg associated with marked subcutaneous neurofibromatosis of this extremity. Note prominence in right supraclavicular fossa due to large cervicothoracic neurofibroma.

left tibia was 4 centimeters longer than the right as measured on the roentgenogram; the tibia had become bowed and the patient's limp was considerably more marked (figure 8).

In February 1938 the patient began to complain of pain and stiffness in the neck. A mass could be seen filling the right supraclavicular fossa and extending upwards to the level of the midportion of the sternocleidomastoid muscle (figure 6).

Roentgen-ray films of the cervicothoracic region (figure 9) at this time showed an egg-shaped soft tissue mass extending from the upper cervical region on the right to the level of the clavicle and across the midline, displacing the trachea markedly to the left. A smaller soft tissue mass could be seen at the base of the neck on the left. Lateral roentgenogram of the cervical spine (figure 10) showed a marked decalcification of the vertebral bodies in the region of the large cervical neurofibroma. These vertebral bodies showed a generally distorted contour and roughening of their

In addition, neurofibromatosis has been known to involve the visceral nerves, especially those of various parts of the gastrointestinal and genitourinary tracts.

Formerly considered a pathological process of rather stationary and quiescent character, this disease at times undergoes active and extensive metamorphosis. Usually the neurofibromata remain stationary in size or grow very slowly. Very rarely the lesions regress spontaneously. At times the pedunculated tumors undergo cystic or myxomatous change, and occasionally the blood supply of the pedicle is compromised and the tumor drops off. The disease may undergo particularly rapid alteration under such physiological stimuli as puberty and pregnancy. There may be slight regression in the size of the lesions at the menopause. Yakovlev and Guthrie particularly have pointed out the dynamic character of the disease with periods of exacerbation and remission in tumor growth. In addition, there is an acute fulminating form characterized by either extremely rapid proliferation and generalized dissemination of neurofibromata or sarcomatous degeneration with metastasis. LeBell maintains that benign neurofibromata undergo malignant transformation in from 12 to 20 per cent of cases following trauma or other irritation. This is in accord with the findings of Sharpe and Young to the effect that sarcomatous change occurs in 13 per cent of all cases. These authors further state that of the cases in which sarcoma develops, metastasis occurs in 22 per cent. Hosoi collected 65 instances of sarcomatous transformation in von Recklinghausen's neurofibromatosis and suggested the danger of inducing such metaplasia by biopsy or inadequate surgery for neurofibromata.

The osseous changes found associated with von Recklinghausen's neurofibromatosis are among the most interesting and often most serious manifestations of this condition. The recognition of such changes dates back to Gould who in 1918 had the opportunity of studying at autopsy the skeletal changes in a patient with generalized cutaneous and subcutaneous neurofibromatosis. A general osteoporosis and decalcification of the pelvis similar to that encountered in osteomalacic pelvis was found. There was no replacement by fibrous tissue as is found in fibrocystic osteitis. The parathyroid glands and hypophysis were studied carefully but no histological changes were found.

In 1921, Weiss called attention to a second variety of bony pathology associated with this disease, namely scoliosis, which he observed in 15 patients with generalized neurofibromatosis. Brooks and Lehmann (1924) reported seven cases of von Recklinghausen's disease with bony changes which they considered characteristic of the disease. These changes were of three types: scoliosis, abnormalities of growth and so-called subperiosteal cysts. In two of their cases there was marked overgrowth of long bones (femur and tibia). When such overgrowth occurs it is usually in areas of elephantiasis. This may be due to periosteal hyperemia associated with the generally increased blood supply necessary to nourish such an elephantiasic

## REVIEW OF THE LITERATURE

Fortunately, von Recklinghausen's neurofibromatosis is a rather rare condition. In 1901 Adrian was able to collect 407 cases from the literature.



FIG. 8. Lateral roentgenogram shows anterior bowing of tibia hypertrophied in association with extensive neurofibromatosis of surrounding soft parts.

Smaller series have been reported by Stalmann and by Sharpe and Young (35 and 31 cases, respectively). Preiser and Davenport, in an exhaustive study of this condition, estimated its incidence in the general population as once in 2000. Among 4300 patients, with proved or suspected benign or



are not infrequently affected similarly. The vertebral changes have been considered so characteristic by Camp as to enable him to localize the level of suspected cord tumors in 42 per cent of cases. According to him, the earliest change is erosion and flattening of the mesial border of the pedicle of the vertebra at the site of the tumor. Later one finds concave areas of erosion on the posterior or posterolateral aspect of the vertebral body itself as the neurofibroma enlarges.

It is to be pointed out that scoliosis may occur in those patients with inequality in length of the lower extremities even in the absence of neurofibromatous involvement of the vertebral column.

### SUMMARY

The authors have presented two cases of von Recklinghausen's neurofibromatosis with osseous changes. The one exhibited marked cystic changes in the mandible, the other gigantism and bowing of the tibia associated with elephantiasis of the lower extremity and osteoporosis, decalcification and atrophy and deformity of the cervical vertebrae in the region of a rapidly growing cervical neurofibroma.

The nature of the disease has been reviewed; it is to be considered of dynamic rather than stationary nature. At the present time no adequate treatment is available for this condition; surgery and radiation are both unsatisfactory. Diagnosis can generally be made without biopsy; in fact, biopsy may sometimes be a dangerous procedure in this condition because of the possibility of inducing sarcomatous metaplasia.

The frequency and seriousness of the bone changes encountered in association with von Recklinghausen's neurofibromatosis have been emphasized. In all cases of the disease, even in the formes frustes without clinical evidence of tumor formation, general roentgen-ray studies are recommended to detect latent osseous changes. Such radiological studies should include the skull, the entire vertebral column and all the bones of the upper and lower extremities.

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115 offspring of 20 patients known to have generalized neurofibromatosis, found a like condition in 43.5 per cent. The development of the condition in the offspring bore no relation to the sex of the parent affected. These authors noted also a familial resemblance in the type and location of the pig-



FIG. 10. Lateral roentgenogram of cervical spine showing decalcification, distortion and atrophy of cervical vertebral bodies adjoining a large cervical neurofibroma.

mentation and cutaneous tumors as well as in the tendency for sarcomatous metaplasia to occur.

One of us (Uhlmann) examined 60 members of three families in which cases of von Recklinghausen's neurofibromatosis had been diagnosed. Of these 60 individuals 13 were found to have the pigmentation and tumor formation characteristic of this disease. In one instance members of three

# STUDIES IN PERNICIOUS ANEMIA: AN INQUIRY INTO THE RÔLE OF PEPSIN \*

By SAMUEL MORRISON, M.D., F.A.C.P., *Baltimore, Maryland*

IN a paper on the mechanism of therapy in pernicious anemia, Greenspon<sup>1</sup> suggested that an "extrinsic factor" as conceived by Castle was unnecessary and that an antianemic principle protected from the inactivating effect of pepsin, such as beef (or other source of "extrinsic factor") was solely essential. This suggestion coincided with our belief that antipernicious anemia potency may be attributed to the fundus as well as to other portions of the stomach, and that this potency is ordinarily neutralized by the action of pepsin, a product primarily of the fundus. Greenspon's contention if confirmed will strongly support our belief.

It has been definitely established that a desiccated defatted hog stomach preparation (*Ventriculin*) has the distinctly antipernicious properties of Castle's "intrinsic factor." Meulengracht<sup>2</sup> has shown with defatted pulverized powders (dried at low temperature) prepared from cardiac, fundus, pyloric and duodenal glands, with muscularis, that the fundus gland preparation was inactive, the cardiac portion mildly active, and the pyloric and duodenal portions were strongly active in antianemic effect. Yet this pyloric gland powder (prepared commercially in Denmark as *Pylorin*) has about the same activity as *Ventriculin*, which is made from the entire stomach.

There are, therefore, two suggestive evidences to support the theory that fundus contains antianemic factor. First, whole stomach should be less potent than pyloric gland preparations if the fundus portion is inert, but this supposition has not been confirmed. Second, if Greenspon's concept of the action of pepsin be true, it may explain the apparent inactivity of the fundus portion. Both *Ventriculin* and *Pylorin* contain protein of the muscularis which acts as an adsorbent of pepsin according to Greenspon, or as a source of extrinsic factor according to Castle. These possibilities led us to repeat Greenspon's work using his depepsinized whole gastric mucosa and in addition, prepared in precisely the same manner, hog's stomach divided into cardiac, fundus and pyloric portions.

In the meantime several reports have appeared which do not substantiate Greenspon, but none definitely refuted the observation that pepsin could, at least partially, inactivate stomach preparations of established antianemic

\* Received for publication June 23, 1937.

In pursuing these studies I have had the coöperation of Dr. Holmes of the University Hospital, Drs. Edwards and Myers of the Church Home and Infirmary, Drs. Rainy, Wyrens and DeSautelle of the City Hospitals, Dr. Freeman of the Mercy Hospital and Dr. Levi of St. Joseph's Hospital, Baltimore. Thanks are also due to Dr. Anderson, Director of the Squibb Laboratories, for his willingness to prepare and supply the depepsinized preparations used in these studies.

The expenses of this investigation were defrayed in part by a grant from the Julius Friedenwald Research Fund of the University of Maryland, School of Medicine.

The skin tumors are the most common and most striking attribute of von Recklinghausen's neurofibromatosis. The gross pattern of such lesions is extremely variable though the histological structure is the same. The most frequent variety is the so-called molluscum fibrosum or soft fibroma of the skin. These are found chiefly on the trunk and less often on the face and extremities. There is tremendous variation in the size and number of these tumors. There may be only a few or thousands; they may be as small as a millet-seed or as large as a man's head. These skin tumors may be sessile, slightly raised, or completely pedunculated. They are usually soft and at times somewhat compressible on palpation, often resting in cavities partly filled with fluid (this is usually associated with myxomatous degeneration of the neurofibroma). There is seldom any pain with such tumors. Rarely, severe pain does occur arising at the site of the skin tumor and radiating in the direction of the cutaneous nerves associated with the tumor in question. On section these neurofibromata are white or whitish-gray and rather translucent. According to Stalmann, who performed biopsies in 35 cases of von Recklinghausen's disease, there is no typical histological pattern. One often finds a palisade-like effect with the nuclei arranged in parallel longitudinal rows. The individual nuclei are elongated and irregular in outline, often containing chromatin resembling the nucleoli of nerve cells. There is considerable diversity of opinion as to the pathogenesis of these skin tumors. This has led to such terms as multiple neuroma, peripheral glioma, schwannoma, neurinoma and perineurial fibroblastoma for one and the same pathological entity. Most authors, however, believe that such tumors are fibromas arising from the connective tissue elements of nerves, particularly from the sheath of Schwann.

In addition to skin tumors, or not infrequently without visible skin tumors, neurofibromata may occur as bead-like subcutaneous nodules along the course of the peripheral nerve trunks. Such subcutaneous nodules are of varying size and distribution but occur most frequently in the neck or extremities. The peripheral nerves most often affected are the median and ulnar of the upper extremity and the sciatic in the lower extremity. These subcutaneous nodules have a rope-like or worm-like consistency and in the neck are often mistaken for cervical lymphadenitis. At times, the larger nerves, such as the spinal or even the cranial nerves, may be involved. The acoustic neuroma is of this type. The cauda equina is a not infrequent location for this variety of tumor. According to Camp, 23 per cent of all spinal cord tumors are neurofibromata. These tumors have also been known to involve the sympathetic and parasympathetic nerves. Histologically, the lesions are of the same structure as the pedunculated cutaneous neurofibromata.

At times the subcutaneous neurofibromatosis assumes an exaggerated contour producing a diffuse swelling of flounce-like nature. This variety of overgrowth is known as the plexiform neuroma, elephantiasis neuromatosa or pachydermatocele.

juice probably contained extrinsic factor which would interact in the period of four hours with the intrinsic factor. They concluded that "normal human gastric juice does not contain an 'anti-pernicious anemia principle' effective on oral administration without contact with food (extrinsic) factor." In another experiment they sustained Greenspon's belief in the destructive action of peptic hydrolysis on an "anti-pernicious anemia principle" because a two hour period of incubation with pepsin was detrimental to intrinsic factor. However, they believe that since removal of pepsin without change in other properties of the gastric juice was not undertaken, their observations do not permit definition of the nature of the destructive process as necessarily peptic hydrolysis. Moreover, they showed that beef muscle and gastric juice administered without opportunity for contact (12 hours) were wholly ineffective.

### THE METHOD OF INQUIRY

The present investigation was so planned that the above criticisms of Greenspon's work could be avoided. Furthermore, it was hoped that the validity of Greenspon's hypothesis could be tested with less error and fewer variables if we used depepsinized gastric mucosa, instead of concentrating on gastric juice. Especially so, since the major part of Greenspon's claim was based on results obtained with it. Our plan was to give depepsinized gastric mucosa orally to a patient whose diet excluded extrinsic factor and then to repeat the experiment with a diet containing adequate extrinsic factor. In so doing, evidence regarding the relative importance of the anti-pernicious anemia principle, intrinsic and extrinsic factors, would be observed, and the importance of pepsin might be surmised. Such an approach we hoped would establish or refute Greenspon's hypothesis. We then planned to carry our observations a step further by attempting to determine the hematopoietic potency of various portions (fundus and pylorus) of the stomach, alone and with the addition of extrinsic factor.

The four patients available for study were typical cases of Addisonian pernicious anemia. All of them were women (ages 64, 53, 50 and 48), all gave evidence of cord changes, and none had been treated. In one (age 48) the cord changes seemed so progressive that liver extract was given before any oral therapy was tried. Her reaction (chart 2) to liver intramuscularly was considered a control with which comparison of the others could be made, inasmuch as the patients were alike even to the degree of anemia. The integrity of intestinal permeability had to be proved, as well as the adequacy of intrinsic and extrinsic factors, before results could be considered of value and we therefore estimated any response to depepsinized oral therapy by comparison with the response to an oral preparation of known potency. This was not always possible but the experiments were so arranged that all observations were cross-checked and in practically every instance the three factors (intrinsic factor, extrinsic factor and intestinal absorption) could be carefully evaluated.

area. Such hypertrophy is circumferential as well as longitudinal and is analogous to the hypertrophy occurring in chronic osteomyelitis or congenital syphilitic periostitis described by Speed. In other cases, especially with pachydermatocele, there may be actual invasion of the bone by neurofibromata. Such involvement may vary from slight irregularity of periosteal or cortical structure to large tumors projecting from the surface of the bone or embedded within the substance of the bone as cyst-like cavities. Microscopic examination of these tumors in one of the cases reported by Brooks and Lehmann showed histologic structure similar to that of the skin tumors. When such neurofibromata actually invade the bone, the osteogenetic periosteum covering the tumor may produce a shell of bone around the tumor resulting in the so-called subperiosteal bone cyst. The radiological appearance of such pseudocysts resembles the findings in osteitis fibrosa cystica, giant cell tumor and xanthomatosis; at times it may be difficult or impossible to differentiate these lesions grossly even at open operation. The entire shaft of the bone may become soft, porous and plastic, with bowing or other deformities, as a result of diffuse neurofibromatous invasion. If the epiphyseal cartilage alone is invaded, shortening and atrophy will result. In isolated zones of periosteal neurofibromatosis, exostoses may develop. In cases with marked decalcification, pathological fractures may occur and heal with pseudoarthroses characteristic of osteopsathyrosis. Deformities such as coxa vara have been described frequently.

Lehmann has commented on the frequency of cystic changes in the skull. Palpable defects of the cranium beneath plexiform neuromas have been reported. Among other changes in the skull are thinning of the cranial vault, atrophy and aplasia of the mandible, maxilla and zygoma. The combination of atrophy and hypertrophy of the various facial bones may produce bizarre distortions, the appearance of leontiasis ossium being not infrequent.

According to Reuben, about 7 per cent of patients with neurofibromatosis show bony changes. Seven of the 31 patients observed by Sharpe and Young exhibited osseous involvement, this being in the nature of scoliosis in six of the seven cases. In six of the patients with bone changes reported by these authors the basal metabolic rate, dextrose tolerance, calcium and phosphorus content of the blood were determined and were found to be within normal limits.

The vertebral column is involved in about 43 per cent of the cases showing skeletal changes according to Miller. The most frequent vertebral change is scoliosis, kyphosis and kyphoscoliosis occurring somewhat less often. The most common site for such change is the lower thoracic spine. Vertebral involvement may be so extensive as to produce compression myelitis (Miller reported such a case with sarcomatous degeneration of the neurofibromata involving the vertebral column). The vertebral column is especially apt to be involved in the presence of neurofibromata of the spinal cord. Such tumors produce pressure on the underlying vertebral bodies with erosion, decalcification and changes in contour. In the thoracic region the ribs

*Experiment 1.* Depepsinized gastric mucosa "Mucex," was secured from the Squibb Laboratories with the consent of Dr. Greenspon and the coöperation of its Director, Dr. Anderson. The dosage advised was 20 gm. a day. In table 1 are recorded the results of such therapy in a patient on a basal diet (as advised by Castle)

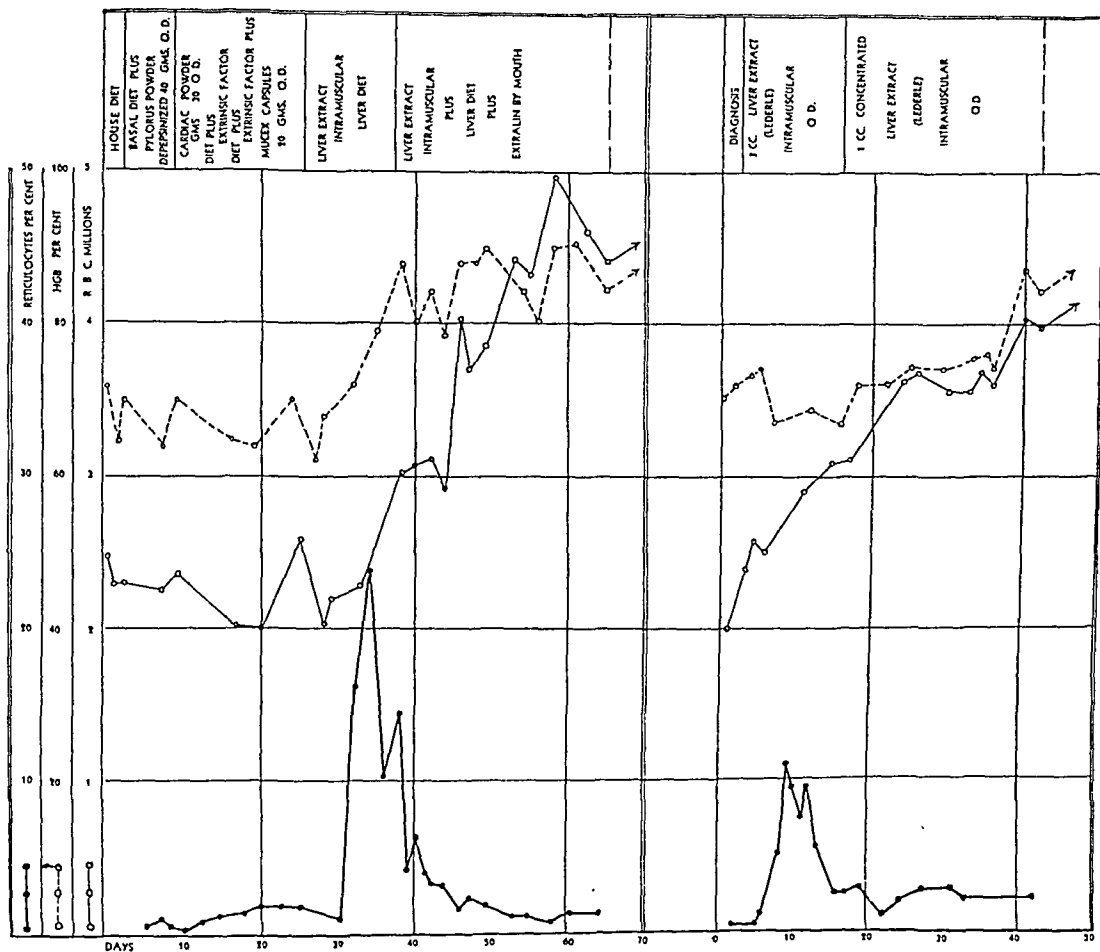


CHART 1. (Left). Patient—E. W.—Age 64.

CHART 2. (Right). Patient—N. S.—Age 48.

excluding every possible source of extrinsic factor. In this instance it was found unnecessary to adhere to the 12 hour interval between feedings although we began by taking that precaution. Compared to these values are those obtained in the second case in which exactly the same procedure was followed except that in the second case the diet contained extrinsic factor, beef, twice daily. No significant reticulocyte response followed in either case nor was there any elevation in hemoglobin or the red blood cell count. The unsustained response in patient I. W. was probably without significance. Assuming dosage was adequate it seems safe to deduce from these observations that depepsinized gastric mucosa prepared from the whole stomach does not contain any antipernicious anemia potency either with or without the addition of extrinsic factor. However, before such a conclusion could be reached the factor of intestinal absorption must be established. As seen in chart 1 this was not possible in patient E. W., in whom postponement of intramuscular liver extract was not justified in view of the cord changes. Her response to liver was characteristic and she has been able to maintain her count by oral "Extralin." This patient may be con-

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significant when interpreted in terms of the comparative antipernicious anemia activity of the various preparations used. Nevertheless, the absence of a response to "Mucex" in the presence of extrinsic factor is presumptive evidence that there would hardly be a response when extrinsic factor was absent.

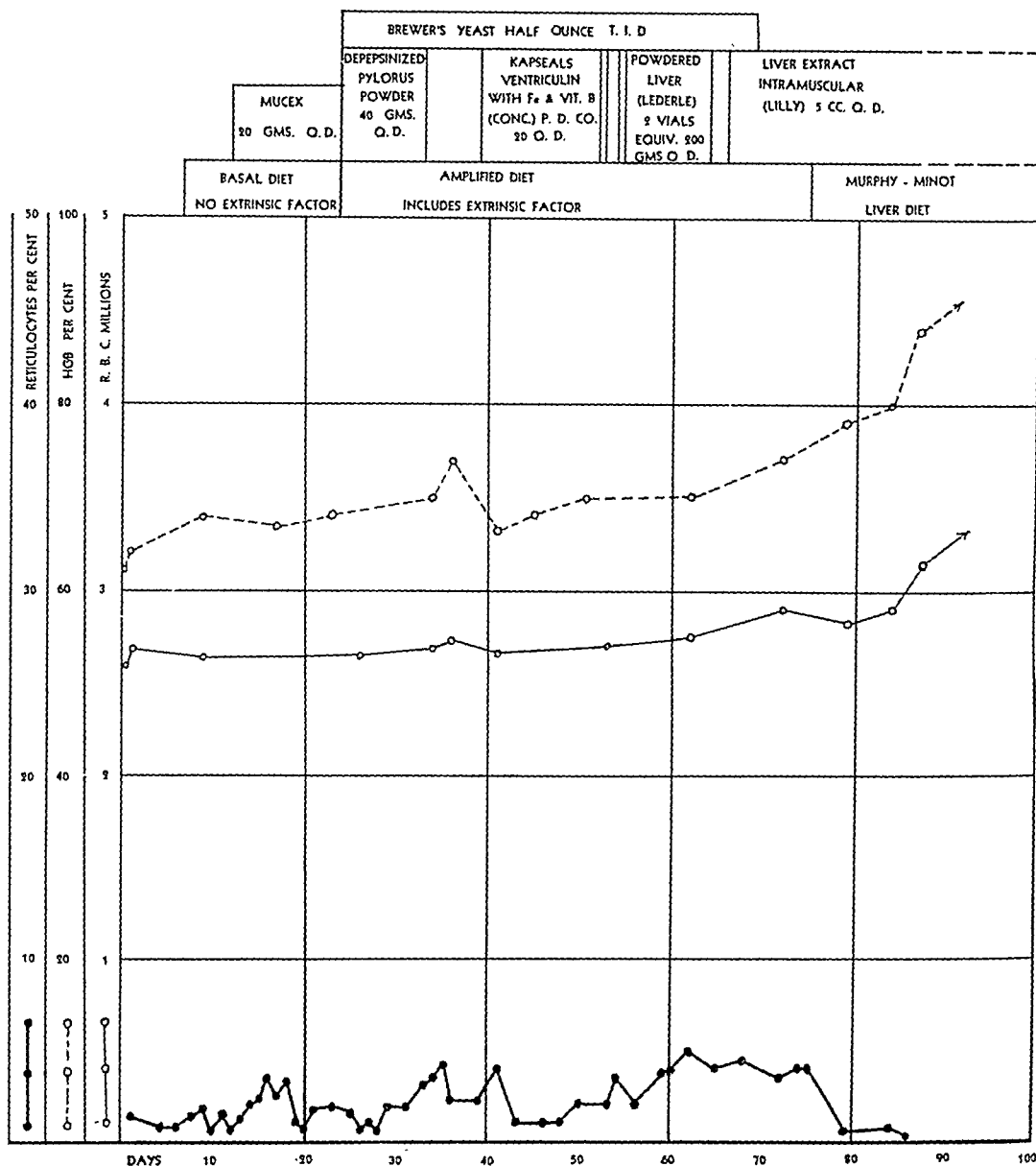


CHART 4. Patient—I. W.—Age 50.

*Experiment 2.* Mucosa stripped from the pylorus of the hog's stomach, observing all precautions for preserving the antianemic factor, was depepsinized according to Greenspon's method. Adequate amounts were fed to two patients; in the diet of one there was a source of extrinsic factor whereas in the other there was none. The data are recorded in table 2. In the latter, patient E. W., there was no reticulocyte response. However, she regurgitated a portion of the first dose (40 gm.) of pylorus

potency. For example, Ungley and Moffett<sup>3</sup> found that peptically inactivated fundus mucosa of pig's stomach when administered with extrinsic factor gave negative results in two cases and a negative but inconclusive result in a third.

On the other hand, pylorus mucosa prepared similarly and administered with a source of extrinsic factor was effective in six cases. Furthermore, they found that orally administered depepsinized gastric juice and pepsin-free extracts of pylorus mucosa had little or no hematopoietic effect unless interaction with a source of extrinsic factor (e.g., autolysed yeast) was allowed. They accordingly concluded that adsorption of pepsin had no effect on extrinsic factor activity since no pepsin was present; also since autolysed yeast required interaction with normal gastric juice or pylorus extract which presumably contained pepsin, to render it effective for blood regeneration, that it probably acts as extrinsic factor and not because "it contains elements that are capable of stimulating the cells that elaborate the gastric anti-anemic agent or because these elements furnish material for the synthesis of the latter" as Greenspon had suggested.

In short, these authors (1) reaffirmed the necessity for both intrinsic and extrinsic factors in hematopoiesis, (2) demonstrated that depepsinized fundus even with extrinsic factor was probably hematopoietically inactive, and (3) that pylorus, under the same conditions, was potent. Conclusive as these experiments appear to be, however, there are two differences between them and the work of Greenspon: the method of preparation of the depepsinized products, and the failure of Ungley and Moffett to use whole stomach mucosa for control as Greenspon had done.

Hanes, Hansen-Prüss and Edwards<sup>4</sup> suggested that the gastric juice feeding experiments could be vitiated by the presence of extrinsic factor in the stomach of the patient or in the gastric juice of the donor. They fed neutralized and chilled gastric juice to five untreated patients with pernicious anemia and observed no hematopoietic potency, but these observations alone would not disprove Greenspon's entire thesis.

A corollary investigation was Fitz-Hugh and Creskoff's<sup>5</sup> study of the effects of depepsinized human gastric juice administered orally and intramuscularly. They point out that Greenspon's patients were not submitted to a (12 hour) fast, that gastric lavage did not immediately precede the gastric juice collections, that the recipients did not receive gastric lavage prior to the administration of gastric juice, and that they were fed too soon (four hours) after gastric juice feedings. Observing these precautions, Fitz-Hugh and Creskoff substantiated neither Morris and co-workers nor Greenspon, as regards the sole importance of "intrinsic factor." They believe, however, that Greenspon is possibly correct in his conclusion that peptic digestion destroys "Ventriculin."

Castle and Ham<sup>6</sup> in their recent "recheck" studies, followed Greenspon's technic except that no ice was put into the gastric juice. They believe that the diet in the patient of Greenspon who responded to neutralized gastric

TABLE III

Comparison of the Effect of Depepsinized Fundus Mucosa with and without Extrinsic Factor

Patient—A. T.				
Days of Treatment	Red Blood Cells Millions	Hemoglobin Per Cent	Reticulocytes Per Cent	Treatment
1	2.45	70	0	Basal Diet
2			0.1	Basal Diet
3			0.2	Basal Diet
4				Basal Diet
5	2.4	71		Basal Diet
6			0.3	Basal Diet + Depep. Fundus 40 gm. q.d.
7			0.2	Basal Diet + Depep. Fundus 40 gm. q.d.
8			0.15	Basal Diet + Depep. Fundus 40 gm. q.d.
9			0.1	Basal Diet + Depep. Fundus 40 gm. q.d.
10			0.2	Basal Diet + Depep. Fundus 40 gm. q.d.
11				Basal Diet + Depep. Fundus 40 gm. q.d.
12	2.3	71	0.4	Basal Diet + Depep. Fundus 40 gm. q.d.
13				Basal Diet + Depep. Fundus 40 gm. q.d.
14			0.2	Basal Diet + Depep. Fundus 40 gm. q.d.
15			0.3	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
16				Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
17			0.2	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
18			0.4	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
19				Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
20			0.3	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
21				Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
22			0.9	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
23			0.3	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
24			0.2	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
25			0.5	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
26			0.3	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
27			0.7	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
28			0.4	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
29	2.18	64	0.3	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
30			0.4	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
31				Amplified Diet
32				Amplified Diet
33			1.5	Amplified Diet
34			0.4	Amplified Diet
35			0.8	Amplified Diet
36			0.5	Amplified Diet

The administration of depepsinized fundus mucosa, prepared by Greenspon's process, in large dosage over a sufficiently long trial period produces no rise in reticulocytes regardless of the presence or absence of extrinsic factor from the diet. In this patient the numerical value of hemoglobin and red blood cells decreased slightly, and the subjective symptoms became more disturbed.

powder administered and only received it for seven days (sufficient according to Greenspon) when, due to an inability to replenish our supply, we were forced to substitute cardia powder for the remaining trial period. This patient responded to liver extract intramuscularly and was maintained on Extralin (chart 1).

In the case of patient I. W., whose diet contained at least two sources of extrinsic factor (beef and brewer's yeast) pyloric powder was fed as seen in table 2 over a period of seven days. On the ninth day before any other therapy had been begun, the reticulocytes had risen in an orderly manner to a peak of 4.3 per cent. This is dis-

TABLE I  
Comparison of the Effect of Mucex \* with and without Extrinsic Factor

Days of Treatment	(Patient—I. W.) Without Extrinsic Factor in Diet				(Patient—E. W.) With Extrinsic Factor in Diet			
	Red Blood Cells Mil- lions	Hemo- globin Per Cent	Reticu- lo- cytes Per Cent	Treatment	Red Blood Cells Mil- lions	Hemo- globin Per Cent	Reticu- lo- cytes Per Cent	Treatment
1			1.1	Basal Diet	2.49	70	0.5	Basal Diet
2			1.8	Basal Diet			0.8	Basal Diet
3	2.61	68	0.5	Basal Diet			1.4	Basal Diet
4			1.3	Basal Diet			1.0	Basal Diet
5			0.5	Basal Diet				Basal Diet
6			1.1	Basal Diet + 20 gm. Mucex q.d.			0.9	Amplified Diet
7			2.0	Basal Diet + 20 gm. Mucex q.d.	2.0	65	1.4	Includes Ext. Factor
8			2.1	Basal Diet + 20 gm. Mucex q.d.			1.8	Includes Ext. Factor
9			3.8	Basal Diet + 20 gm. Mucex q.d.			1.4	Includes Ext. Factor + 20 gm. Mucex q.d.
10			2.5	Basal Diet + 20 gm. Mucex q.d.			1.8	Includes Ext. Factor + 20 gm. Mucex q.d.
11		67	3.2	Basal Diet + 20 gm. Mucex q.d.	2.0	74	1.8	Includes Ext. Factor + 20 gm. Mucex q.d.
12			1.0	Basal Diet + 20 gm. Mucex q.d.			1.5	Includes Ext. Factor + 20 gm. Mucex q.d.
13			0.9	Basal Diet + 20 gm. Mucex q.d.				Includes Ext. Factor + 20 gm. Mucex q.d.
14			1.8	Basal Diet + 20 gm. Mucex q.d.			1.3	Includes Ext. Factor + 20 gm. Mucex q.d.
15			2.0	Basal Diet + 20 gm. Mucex q.d.			1.6	Includes Ext. Factor + 20 gm. Mucex q.d.
16				Basal Diet + 20 gm. Mucex q.d.			1.5	Includes Ext. Factor + 20 gm. Mucex q.d.
17			1.4	Basal Diet + 20 gm. Mucex q.d.	2.58	70	1.1	Includes Ext. Factor + 20 gm. Mucex q.d.
18	2.63	68	0.8	Amplified Diet Extrinsic Factor Added			0.8	Includes Ext. Factor + 20 gm. Mucex q.d.
19			1.0	Amplified Diet Extrinsic Factor Added	2.01	62		Includes Ext. Factor
20			0.9	Amplified Diet Extrinsic Factor Added				Includes Ext. Factor
21	2.65	69	2.0	Amplified Diet Extrinsic Factor Added	2.2	66	0.7	Includes Ext. Factor

\* Mucex is the name given Greenspon's depepsinized whole stomach mucosa.

The administration of mucex over a period of 10 days—20 grams each day, does not produce a reticulocyte response in patient E. W. whose diet contained sources of extrinsic factor (adequate beef and other foods with the exception of those containing intrinsic factor). The reticulocyte response in patient I. W., whose diet was lacking in sources of extrinsic factor, is neither marked, orderly nor maintained and is not followed by a rise in hemoglobin or red blood cells during a period of observation considerably longer than is shown.

Although Meulengracht reported antipernicious anemia potency in the entire pyloric-gland region (including cardia and duodenum), Henning and Brugsch,<sup>8</sup> using only mucosa (Meulengracht's preparations contained mucosa plus muscularis) conclude from their investigations that powder prepared from the mucous membrane of the antrum was far superior to those from the cardia, fundus and duodenum and in fact the latter group did not produce any reticulocytosis. Gutzeit and Herrmann<sup>9</sup> found that powder from the fundus mucosa of hog's stomach caused a reticulocyte rise in pernicious anemia more regularly than powder prepared from pyloric mucosa. Moreover, Henning and Stieger<sup>10</sup> reported that by trying the mucous membrane of the body of the stomach and that of the pylorus separately they found both possessed the same blood regenerating power, and by proving that neither the one nor the other possessed a peptic ferment of any account in vitro, they believed they had confirmed the assumption that the effect of the powder was independent of peptic digestion or protein and was a primary and direct one on blood regeneration. It was as late as 1934 that Henning<sup>11</sup> definitely concluded that the pyloric antrum produced a substance which, in normal individuals, prevented the development of pernicious anemia.

Of further interest is Lim's consideration of whether or not the pyloric principle which he investigated is identical with histamine. It seemed likely to him, as it did to Keeton, Koch and Luckhardt, that the pyloric principle, or gastrin, is closely allied to histamine; at least the effect on the gastric secretion and motility is remarkably similar. Furthermore, Lim believes that "the localization of the excitant mainly in the pylorus and to some extent in the cardia and duodenum suggests a correlation between the distribution of the excitant and the histological structure. The cardiac and pyloric glands are, according to Bensley and others, identical in structure, while Brunner's glands in the duodenum are considered vagrant pyloric elements. These are composed entirely of 'mucoïd cells' and it seems not unlikely that the gastric excitant has been extracted from these elements. Mucoïd cells also occur in the walls of the fundus glands, but here they are fewer in number as they are mingled with peptic and oxyntic cells. This admixture may be the reason why fundus extracts, made by the simple procedures described here, were comparatively inert, while the more complex extractions employed by Popielski, Keeton and Koch may account for the success which they obtained, with their fundus preparations." Although Lim was not even remotely concerned with the subject of pernicious anemia his description of the pyloric principle and the anatomical relationships of the various portions of the gastro-duodenal region is so strikingly similar to that of Meulengracht that one is led to conclude that fundamentally the problem is basically the same in each instance.

#### SUMMARY

According to Greenspon, pepsin is antagonistic to the antipernicious anemia factor in stomach (Castle's "intrinsic factor"). Pepsin is pre-

sidered a test case. It is interesting to note that her response (23.7 per cent reticulocytes) to intramuscular liver exceeds the expected maximum suggesting that perhaps preceding therapy may possibly have been partly responsible by either conditioning the blood-forming tissues, or by its own delayed reaction.

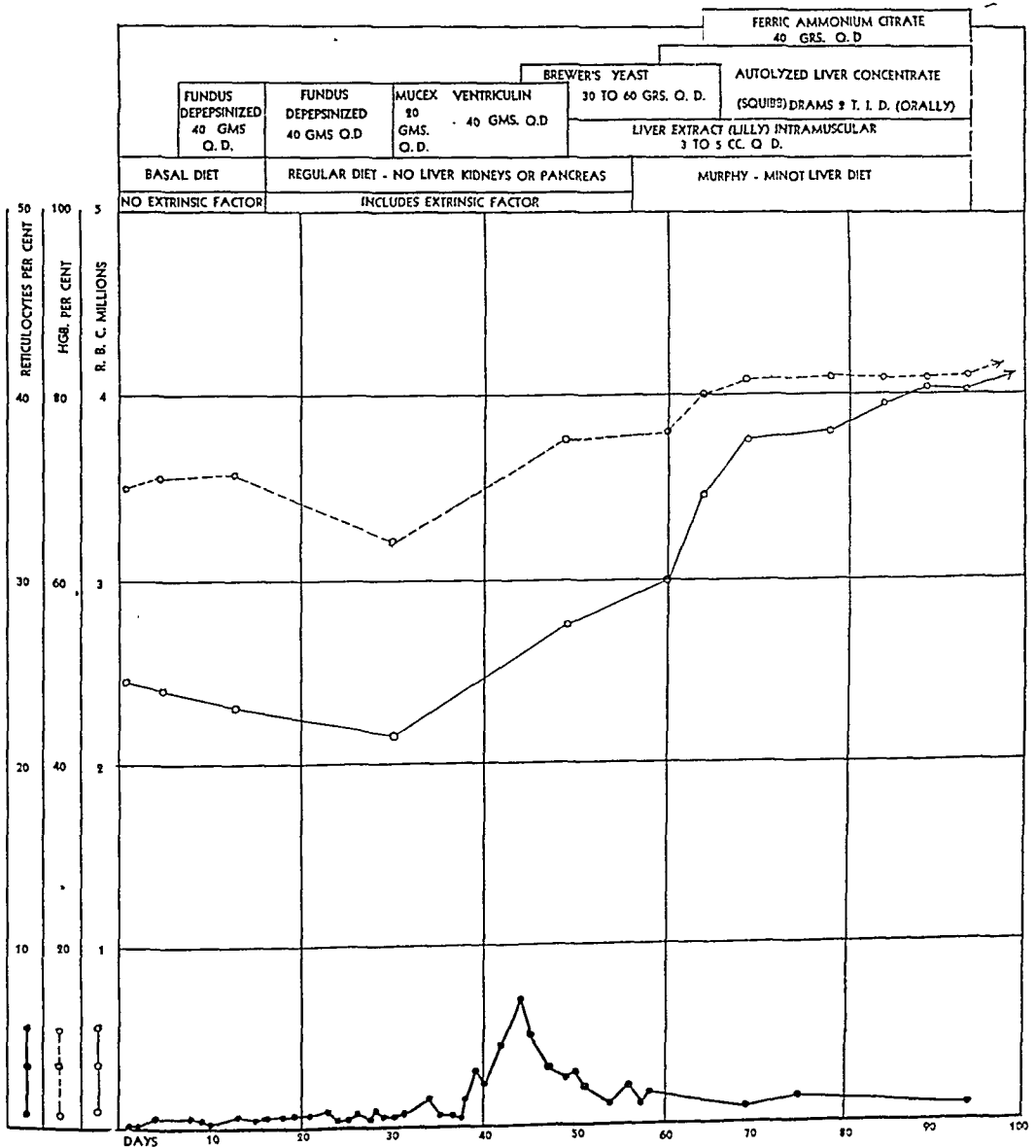


CHART 3. Patient—A. T.—Age 53.

In patient I. W., an interesting observation was recorded (chart 4). Her reticulocyte response to submaximal doses of Ventriculin and oral powdered liver extract were submaximal and these responses were not followed by subsequent characteristic rises in hemoglobin and red blood cell count although the latter may have been prevented by discontinuing therapy for a short period so that the reticulocyte gauge of therapeutic activity might be retained. Moreover, the response to liver extract intramuscularly was delayed and submaximal. All of these submaximal responses may be

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TABLE II  
Comparison of the Effect of Depepsinized Pyloric Mucosa with and without Extrinsic Factor

Patient—E. W. Without Extrinsic Factor					Patient—I. W. With Extrinsic Factor				
Treatment					Treatment				
Days of Treatment	Red Blood Cells Millions	Hemoglobin Per Cent	Reticulocytes Per Cent		Red Blood Cells Millions	Hemoglobin Per Cent	Reticulocytes Per Cent		
1	2.48	72		House Diet	2.62	68	2.0	Basal Diet	
2	2.30	68		House Diet				Basal Diet	
3	2.29	70		House Diet	2.63	68	1.4	Basal Diet	
4				Basal Diet + Depep. Pylorus 40 gm. q.d.			0.8	Amplified Diet (Includes Ext. Factor)	+ Depep. Pylorus 40 gm. q.d.
5			0.5	Basal Diet + Depep. Pylorus 40 gm. q.d.				Amplified Diet (Includes Ext. Factor)	+ Depep. Pylorus 40 gm. q.d.
6			0.7	Basal Diet + Depep. Pylorus 40 gm. q.d.				Amplified Diet (Includes Ext. Factor)	+ Depep. Pylorus 40 gm. q.d.
7				Basal Diet + Depep. Pylorus 40 gm. q.d.				Amplified Diet (Includes Ext. Factor)	+ Depep. Pylorus 40 gm. q.d.
8	2.2	63	0.3	Basal Diet + Depep. Pylorus 40 gm. q.d.			2.0	Amplified Diet (Includes Ext. Factor)	+ Depep. Pylorus 40 gm. q.d.
9			0.5	Basal Diet + Depep. Pylorus 40 gm. q.d.				Amplified Diet (Includes Ext. Factor)	+ Depep. Pylorus 40 gm. q.d.
10	2.49	70	0.5	Basal Diet + Depep. Pylorus 40 gm. q.d.	2.67			Amplified Diet (Includes Ext. Factor)	+ Depep. Pylorus 40 gm. q.d.
11			0.8	Basal Diet + Depep. Pylorus 40 gm. q.d.			3.3	Amplified Diet (Includes Ext. Factor)	+ Depep. Pylorus 40 gm. q.d.
12			1.4	Basal Diet + Depep. Cardia* 40 gm. q.d.		70	3.5	Amplified Diet (Includes Ext. Factor)	+ Depep. Pylorus 40 gm. q.d.
13			1.0	Basal Diet + Depep. Cardia* 40 gm. q.d.	2.71		4.3	Amplified Diet (Includes Ext. Factor)	
14				Basal Diet + Depep. Cardia* 40 gm. q.d.		74	2.0	Amplified Diet (Includes Ext. Factor)	
15			0.9	Basal Diet + Depep. Cardia* 40 gm. q.d.				Amplified Diet (Includes Ext. Factor)	
16	2.0	65	1.4	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)	
17			1.8	Amplified Diet (Includes Ext. Factor)			2.0	Amplified Diet (Includes Ext. Factor)	
18			1.4	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)	
19			1.8	Amplified Diet (Includes Ext. Factor)	2.65	66	4.0	Amplified Diet (Includes Ext. Factor)	
20	2.0	74	1.5	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)	
21				Amplified Diet (Includes Ext. Factor)			1.0	Amplified Diet (Includes Ext. Factor)	
22			1.3	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)	
23			1.6	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)	
24			1.5	Amplified Diet (Includes Ext. Factor)			1.0	Amplified Diet (Includes Ext. Factor)	
25	2.58	70	1.1	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)	
26			0.8	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)	
27				Amplified Diet (Includes Ext. Factor)		68	1.0	Amplified Diet (Includes Ext. Factor)	
28	2.01	62		Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)	
29				Amplified Diet (Includes Ext. Factor)			2.0	Amplified Diet (Includes Ext. Factor)	
30	2.2	66	0.7	Amplified Diet (Includes Ext. Factor)	2.67	69	2.0	Amplified Diet (Includes Ext. Factor)	

\* Cardia depepsinized mucosa was used because supply of pyloric material could not be replenished in time. The administration of depepsinized pylorus mucosa to patient E. W. whose diet did not include extrinsic factor, did not produce a reticulocyte response. On one occasion this patient regurgitated a portion of the material. This fact added to the substitution of cardia for pylorus material makes it desirable to repeat these observations. In the case of I. W., a small reticulocyte response is noted. This, together with the slight elevation in red blood cells and hemoglobin values must be interpreted as indicative of a minimal antipernicious anemia potency.



followed by the appearance of a traumatic pancreatic cyst which was removed. At the time of this operation his spleen was not enlarged and his blood count was normal. After this operation, he developed, over a period of three years, a slowly progressive splenomegaly with falling peripheral blood values until 1931 when the clinical diagnosis of Banti's disease was fully apparent. Splenectomy by Dr. Whipple on June 2, 1932, showed a very large spleen with dilated, tortuous portal vessels. The splenic vein entered the scar of the pancreatic operation at which point the blood flow in the vein was seriously impeded by a constricting band of dense connective tissue. The liver appeared normal. The patient made an uneventful recovery, his blood values promptly returned to normal and he has been without symptoms for eight years. His blood is normal, and there has been no clinical evidence of liver disease. It was obvious to all of us who followed this patient that we were dealing with a purely mechanical situation that had resulted in a clinical and histological picture indistinguishable from the Banti syndrome. Because of the presence of such an obvious mechanical factor in this case, and because of the gross appearance of the portal system at operation in other cases, we began to wonder if obstruction to the flow of splenic vein blood might not be an important element in the production of this syndrome. The promptness with which the splenomegaly may vanish after hematemesis was further evidence of venous tension, and as new cases came to operation we noticed a variety of different lesions associated with this syndrome. Some of these lesions were intrahepatic, others were extrahepatic, but all could produce splenic vein hypertension.

The possibility that chronic splenomegaly might result from some interference with the flow of portal blood has been mentioned by several authors. Eppinger<sup>2</sup> and Warthin<sup>3</sup> both suggested that at least in some cases of splenic anemia a mechanical factor appeared to exist. McMichael<sup>4</sup> refers to the importance of portal hypertension in some cases of splenomegaly and he and McNee<sup>5</sup> both discuss the possible importance of this factor in the production of Banti's disease. But nowhere in these papers can one find a definite statement presenting this factor as the actual cause of this clinical picture.

The results of our studies on the splenic vein pressure levels in this syndrome have been published.<sup>6</sup> When compared with the venous pressure in the peripheral circulation or with the splenic vein pressures in other types of splenomegaly there is no doubt but that splenic vein hypertension, of great magnitude, is an important and invariably present factor in this disturbance. Table 1 shows these readings.

In 1936 and 1939<sup>7,8</sup> Rousselot reported on the importance of this mechanical factor in our earlier cases. He stated the tentative views of the Spleen Clinic group on the pathogenesis of the syndrome at that time. Further study of an increasingly large number of cases has tended to extend and clarify this idea.

It is our current concept that Banti's disease, or splenic anemia, is the result of mechanical obstruction to the flow of blood within the portal system.

tinctly a submaximal response and was followed by a minor increase in red cell count and hemoglobin which can be interpreted as manifesting the presence of some anti-pernicious anemia potency. This patient also responded submaximally to both Ventriculin and oral powdered liver of known potency (chart 4). The experiment suggests that pylorus powder is not potent in the absence of extrinsic factor, and is potent with it.

*Experiment 3.* Depepsinized fundus mucosa was administered to patient A. T., without extrinsic factor. The results are recorded in table 3. There was no reticulocyte response and no change in either hemoglobin or red cell count. After this negative response an amplified diet including extrinsic factor was given and the depepsinized fundus substance was continued, without effect. There was, however, a satisfactory reticulocyte response (7 per cent) to Ventriculin (chart 3), and intestinal absorption was apparently satisfactory.

## DISCUSSION

Intestinal permeability is an extremely important, and perhaps uncertain, factor in determining the potency of oral preparations. The amount of material administered cannot by any means be considered the amount absorbed, for not only may there be a defect in intestinal absorption but diarrhea or vomiting may impair its effectiveness. Depepsinized preparations were extremely unpleasant in taste and smell. Perhaps the intestine may have reacted to them as foreign bodies in the unrefined form in which they were administered and have rejected them. Only "Mucex" was administered in capsules, the others in "revolting" powders.

The failure to disclose significant antipernicious anemia potencies in any of these depepsinized preparations should be considered not only in terms of insufficient intrinsic factor and extrinsic factor, but also in terms of intestinal impermeability. Any deficiency in the latter interferes with the absorption of both factors and also of antipernicious anemia principle, if such it be. Moreover the method of preparation of those materials, though yielding the potent products described in Greenspon's original report, may conceivably be responsible for the total or partial inactivity of these later preparations. This was suggested by Lim<sup>7</sup> whose work on gastrin seems applicable here and worthy of recalling. Lim found that the activity of the extracts in producing gastric secretion depended in a measure on their mode of preparation and he concluded that the potency of extracts of the mucous membrane of the stomach and small intestine is of the following descending potency: pyloric, cardiac, duodenal, fundic, jejunal and ileal. Pyloric extracts almost invariably produced the standard effect, cardiac and duodenal extracts sometimes, and the other extracts never. This is an important observation in the light of Meulengracht's recent work. The observations of Edkins and Maydell are mainly confirmed by Lim, while those of Popielski and others are not refuted. Indeed, it seems probable that, by adopting different methods of extraction, the order of potency could be so altered as to obtain results similar to those of Popielski, who found fundus extracts to be as active as those of the pylorus.

explains the collateral circulation. With high portal pressure and relatively low peripheral venous pressure, a reversal in the direction of normal blood flow can take place in at least part of the portal system. This reversal in direction of blood flow is the direct result of the abnormal hemodynamics that exist in these cases and is permitted to occur by the absence of valves in the portal system.

A careful review of our clinical material leads to the conclusion that there are no significant differences, clinical or hematological, between the congestive splenomegalies resulting from the various obstructive factors. Variations may occur in the velocity of progress, depending upon the nature of the underlying disturbance, but the basic disease pattern is the same in all of our subdivisions.

Of equal importance is the fact that the splenic histology is the same in all groups. A recent review of the microscopic sections of 68 spleens of patients with congestive splenomegaly has led Dr. H. D. Kesten, of the Department of Pathology, and myself to the conclusion that no detectable histologic differences exist between the spleens of the various subdivisions of this syndrome. All show variable degrees of follicular atrophy; all present fibrosis of the pulp with dilated venous sinuses; all have the very characteristic perifollicular hemorrhages. The presence of siderotic nodules would seem to depend largely upon the accidental inclusion of one or more in any given section.

The obstructive lesions that are responsible for this secondary congestive splenomegaly are divisible into two main groups: intrahepatic and extrahepatic.

The intrahepatic lesion responsible for congestive splenomegaly is cirrhosis. Of our total group, hepatic cirrhosis was present as the obstructive factor in 68 per cent.

Scarring of the liver causes increased portal pressure in two ways. First, there is an increased resistance to the flow of portal blood through the liver caused by the constricting bands of periportal connective tissue. Second, there is a distortion of the normal hepatic artery—portal vein anastomoses—that permits the transmission of arteriolar pressures to portal vein radicals.

The double mechanism has been carefully studied by others. Perfusion experiments in normal and cirrhotic livers<sup>9</sup> and histologic studies of the intrahepatic vascular bed<sup>10</sup> in normal and scarred organs show that this conclusion may be accepted.

Of chief concern to us is the question of the relation between the type of hepatic scarring and the degree of portal hypertension. Cirrhosis, in general, tends to be associated with splenomegaly of the congestive type. The amount of splenomegaly, however, is variable and it is important to try to determine what types of cirrhosis result in Banti's disease and what types do not.

We have studied this question from various angles, with the assistance

dominantly a product of the fundus portion of the stomach. Hence, we assumed that the failure to demonstrate antipernicious anemia effectiveness in fundus tissues could be attributed to their pepsin content. To test this hypothesis the three cases here reported were treated with depepsinized whole stomach mucosa and depepsinized fundus and pylorus mucosa, obtained from the hog's stomach under proper conditions for preserving antipernicious anemia potency according to Greenspon. The treatment of the patients was checked in such a fashion that significant results were obtained. In considering these results the attempt was made to evaluate the relative rôles of intrinsic factor, extrinsic factor and intestinal permeability. The absorptive ability of the intestinal mucosa is a rather uncertain factor in cases of pernicious anemia since it is not altogether unlikely that the morbid process underlying the disease also produces impairment of cell permeability. Perhaps this is one reason for the greater potency of intramuscular preparations.

### CONCLUSIONS

1. The feeding of depepsinized whole stomach mucosa, "Mucex," with and without the addition of extrinsic factor, was not significantly effective in pernicious anemia.

2. The feeding of depepsinized fundus mucosa with and without the addition of extrinsic factor, was not effective in pernicious anemia.

3. The feeding of depepsinized pyloric mucosa without the addition of extrinsic factor was not effective. However, when extrinsic factor was added there was a minimal, though definite, evidence of antipernicious anemia activity.

4. Intestinal permeability is often impaired as is shown by the submaximal responses to the administration of oral preparations of known activity.

5. The claim for higher activation by depepsinization by Greenspon has not been sustained. His conception of the existence of an antipernicious anemia principle, excluding the action of the extrinsic factor, has not been confirmed.

6. The possibility of completely depepsinizing fundus tissues by present methods is debatable. Perhaps this explains the complete inactivity of fundus preparations.

7. The suggestion is made that the process of depepsinization may not always result in the same end-product. In one instance an active product may be obtained, in another an inactive one. Therefore, the investigations here reported only suggest a refutation of Greenspon's findings.

8. Unless disproved, Greenspon's demonstration of the antagonism of pepsin toward the antipernicious anemia factor (Castle's intrinsic factor) considered along with the known adsorptive capacity of protein for pepsin and coupled with the histological knowledge of peptic cell predominance in the fundus of the stomach suggests a rôle for the fundus in pernicious anemia. This is now under investigation.

of congestive splenomegalies secondary to hepatic scarring is that when cirrhosis, if looked for, does not exist as the obstructive agent at the time of splenectomy, it will not appear subsequently. We have yet to see a patient develop the sequence of events characterized by Banti as the three stages of this syndrome. Cirrhosis exists in over half of our cases as the obstructive factor; in the remainder the obstruction to the portal flow lies elsewhere and evidence of cirrhosis does not appear even after years of careful clinical study or at subsequent autopsy.

The extrahepatic lesions responsible for congestive splenomegaly are many and varied. Thrombosis of the portal or splenic veins may occur as a result of injury or infection and we have several examples of Banti's disease, typical in all respects, resulting from this obstructive lesion.

The peculiar lesion known as cavernomatous transformation of the portal vein, with or without an underlying thrombosis, has been present as the obstructive mechanism in two cases. Compression of the splenic vein by tumors and scars is a rare cause of this syndrome. And we have been interested recently in a group of 30 patients who have developed the Banti syndrome during childhood. In about 50 per cent of this younger age group, Laennec's cirrhosis of the liver has been present as the obstructive mechanism. In others a definite obstructive factor has not been found at operation and most of these patients ultimately have died of hematemeses. As several of these juvenile patients developed evidences of congestive splenomegaly before the age of one year, we have wondered if the obstructive mechanism might not be a defect in the portal vein, either an anatomical developmental defect or a thrombosis occurring at the time of birth coincident with the thrombosis of the umbilical vein, as a result of this normal process extending beyond its usual limits.

As only four of this younger extrahepatic group have come to autopsy we cannot be absolutely sure of the obstructive mechanism in all. But in these four a stenosis of the portal vein was found as the cause of the portal hypertension. The site of the stenosis and its apparent duration suggest that it occurred either shortly before or just after birth. Rousselot, in a recent report to the Society of University Surgeons, states that he believes that this lesion is responsible for the non-cirrhotic group of Banti's syndrome that occurs in infancy and childhood. It is an interesting lesion and deserves further study.

Certain statements can be made with respect to this whole group of cases :

1. Direct or indirect evidence of portal vein hypertension exists as the common denominator in all cases of so-called Banti's disease or splenic anemia.
2. This portal hypertension in the presence of normal peripheral venous pressure results in the splenomegaly, the collateral circulation, and the esophageal varices.

# THE PATHOGENESIS OF BANTI'S DISEASE\*

By WILLIAM P. THOMPSON, M.D., *New York City*

IN 1883 Banti wrote a monograph entitled "dell Anemia Splenica." In this monograph he described a group of cases presenting splenomegaly with anemia and leukopenia. A particular and, to him, pathognomonic histologic change appeared in the spleen and he insisted that the disease resulted from the activities of some unknown toxic agent that irritated first the spleen and secondarily the liver.

In the next 10 years 10 more papers were written by Banti on this syndrome; his name became firmly attached and the syndrome entered the medical texts as Banti's disease.

In this country Osler published several papers—the first in 1900—on this disease picture. The clinical pattern, as defined by him, remains as the standard definition in subsequent textbooks of medicine.

This definition of Banti's disease, or splenic anemia, reads as follows: "An intoxication of unknown nature characterized by great chronicity. There is a primary progressive enlargement of the spleen which cannot be correlated with any known cause, anemia of the secondary type with leukopenia—a marked tendency to hemorrhage from the lower oesophagus and a terminal state with cirrhosis of the liver."

The members of the Spleen Clinic at the Presbyterian Hospital have, for the past 10 years, been particularly interested in this syndrome. During these years we have had the unusual opportunity of observing 137 cases of this general type. Of this total group 100 have been followed for a sufficient number of years, under circumstances that are nearly ideal for clinical investigation.<sup>1</sup> Splenectomies have been done in 68 instances. As a result of this 10 year study, our view of this condition has altered. A concept of the pathogenesis of the syndrome has developed which is different from that generally accepted and is presented here for the first time.

Early in our study it became necessary to agree upon the criteria by which patients could be placed into this clinical group. These criteria can be stated as follows: Splenomegaly with anemia, leukopenia and thrombocytopenia with evidence of the development of increased collateral circulation between the portal and peripheral venous circulation and histologic changes in the spleen that are characteristic.

The first intimation that the accepted concept should be questioned occurred early in our studies with the appearance of a patient, E. W., Unit No. 318773. This patient was a young, healthy, vigorous policeman who in 1928 suffered an epigastric injury as a result of accident. The injury was

\* Read at the Cleveland meeting of the American College of Physicians April 2, 1940.

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TABLE I  
Venous Pressures in Millimeters of Normal Saline  
Banti—*Laennec Cirrhosis*

Pt.	Splenic Vein	Arm Vein
C. M.	225	12
C. M.	325	85
D. P.	450	125
N. A.	470	145
R. B.	370	30
S. S.	360	150
G. A.	260	190

Banti—*Thrombosis of Splenic Vein*

Pt.	Splenic Vein	Arm Vein
J. S.	390	170

Banti—*Schistosomiasis Mansoni*

Pt.	Splenic Vein	Arm Vein
P. R.	250	50
A. E.	335	105
G. P.	500+	70
C. C.	415	125
L. M.	375	60
H. B.	377	110

Banti—*Obstructive Factor Undetermined*

Pt.	Splenic Vein	Arm Vein
L. D.	275	105
C. K.	370	50
B. S.	330	55
P. M.	465	110

Controls

Pt.	Splenic Vein	Arm Vein	Diagnosis
F. H.	190	65	Lymphosarcoma
R. B.	105	80	Hemolytic jaundice
L. L.	220	205	Atypical hemolytic jaundice
N. B.	125	130	Hemolytic jaundice
S. S.	215	40	(shock) Gaucher's
L. L.	190	107	Splenomegaly of undetermined origin
W. U.	120	95	Hemolytic jaundice
S. J.	360	—5	(severe shock) Purpura
Z. G.	185	75	(beginning shock) Pancreatic adenoma
S. L.	190	210	Purpura
G. C.	235	165	Splenomegaly of undetermined origin
E. N.	275	205	Atypical hemolytic jaundice
T. K.	70	300	Purpura
M. M.	140	65	Purpura
J. K.	245	240	Lymphatic leukemia
A. M.	175	125	Splenomegaly of undetermined origin
J. B.	225	185	Hemolytic jaundice
H. A.	180	20	(in shock) Reticulo-endotheliosis
H. R.	290	290	Giant foll. hyperplasia
S. R.	180	165	Hemolytic jaundice

The site and character of the obstruction must be such that a chronic increase in splenic vein pressure will occur. At the same time the venous pressure in the peripheral circuit should be approximately normal. This differential in heads of pressure is, we believe, the actual cause of the splenomegaly and



frequently encountered than were bloods with an iron level above this figure. In other words, a slight or moderate degree of blood-iron deficiency was more commonly found than a corresponding degree of iron plethora.

The value of 47 mg. per 100 c.c., although the mode of this series, should not be considered as a strictly normal average blood-iron value. The pa-

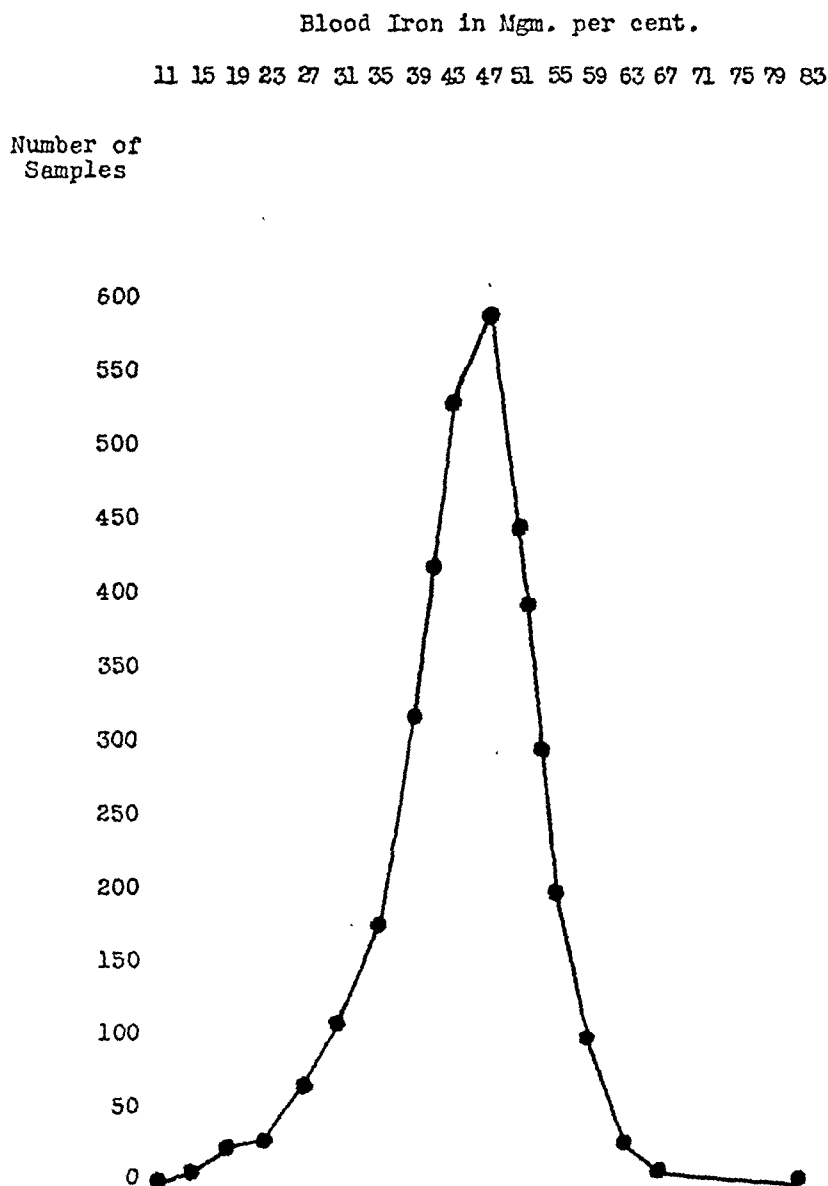


FIG. 1. The blood-iron level in 2608 blood samples. The readings for convenience have been grouped in successive steps of 4 mg. per 100 c.c. of blood.

tients in this series were not normal but were sufficiently ill to warrant admission to a hospital. A study of normal subjects by Sachs, Levine and Fabian<sup>3</sup> has established the normal blood-iron level for males at about 50 mg. per 100 c.c., and for females at about 43.5 mg.

of qualified pathologists and clinicians. Our current conclusions may be summarized as follows:

(1) The type of hepatic scarring seen in prolonged schistosomiasis results in the greatest increase in portal pressures and the largest spleens. The behavior of this parasitic disease is ideal for the production of portal hypertension. The adult worms reside in the pelvic and perirectal radicals of the portal system. The large spiked ova drift with the blood flow into the smaller intrahepatic portal vessels where they lodge, disintegrate, and set up the typical "pipe stem" type of scarring. The ova do not reach the spleen, in our experience, except in massive infestations. This slowly progressive distortion of the intrahepatic radicals of the portal vein results in a slowly rising portal vein pressure. Secondary to this portal hypertension there develops the typical clinical and pathological picture of Banti's disease and it is this sequence that is responsible for much of the splenic enlargement seen in Egypt,<sup>11</sup> China<sup>12</sup> and the Caribbean area.<sup>13</sup>

A similar sequence of events has been produced experimentally by Roussetot and myself<sup>14</sup> by injecting silica particles into the splenic veins of dogs. Here again, the slowly progressive periportal scarring produces rising portal pressures and results, after two years, in congestive splenomegaly with extensive collateral circulation.

(2) In our experience, biliary cirrhosis and cardiac cirrhosis do not produce congestive splenomegaly. Very rarely, prolonged cardiac decompensation may produce unusually dense hepatic scars with resultant portal hypertension and mild splenomegaly of the Banti type.

(3) Periportal cirrhosis of the Laennec type results in a variable degree of splenomegaly. A recent review of 81 autopsied cases reveals certain interesting and important correlations between the type of hepatic scarring and the amount of portal hypertension. Approximately 60 per cent of the 81 cases recorded as Laennec cirrhosis in the files of the Department of Pathology have an associated splenomegaly of the Banti type and esophageal varices. In this 60 per cent the periportal scars are dense, there is great distortion of the intrahepatic vascular bed, and there is minimal evidence of liver cell damage. Many of these patients present the clinical features of Banti's disease and many ultimately die of hemorrhage from rupture of the esophageal varices. In the remaining 40 per cent there is less connective tissue, less distortion of the vascular bed, and more evidence of injury of the liver parenchyma, and these individuals die of hepatic insufficiency with clinical cholemia. Intermediate stages between these two types exist, but we feel we can predict, with considerable assurance, the degree of splenomegaly in any case from examination of the microscopic section of the liver. It is wise to remember that the important lesion is in the liver and that the extent, type, and velocity of progress of the liver lesion is what determines the prognosis of the patient's disease.

One other statement that can be made with respect to this whole group

Barkan and Schales,<sup>6</sup> previously designated by Barkan<sup>7</sup> as "leicht abspaltbares Bluteisen." The greatest single factor, then, influencing the total iron of the blood is the amount of hemoglobin present, accounting for 85 to 95 per cent (usually the latter) of the total iron. In a rough fashion the interpretation of blood-iron values is comparable to the interpretation of hemoglobin values; exact agreement is not obtained on account of the presence of varying amounts of non-hemoglobin iron, even when the method used for the measurement of hemoglobin is comparable in accuracy with that used for iron, as in the work reported by Klumpp.<sup>8</sup> The customary methods for the

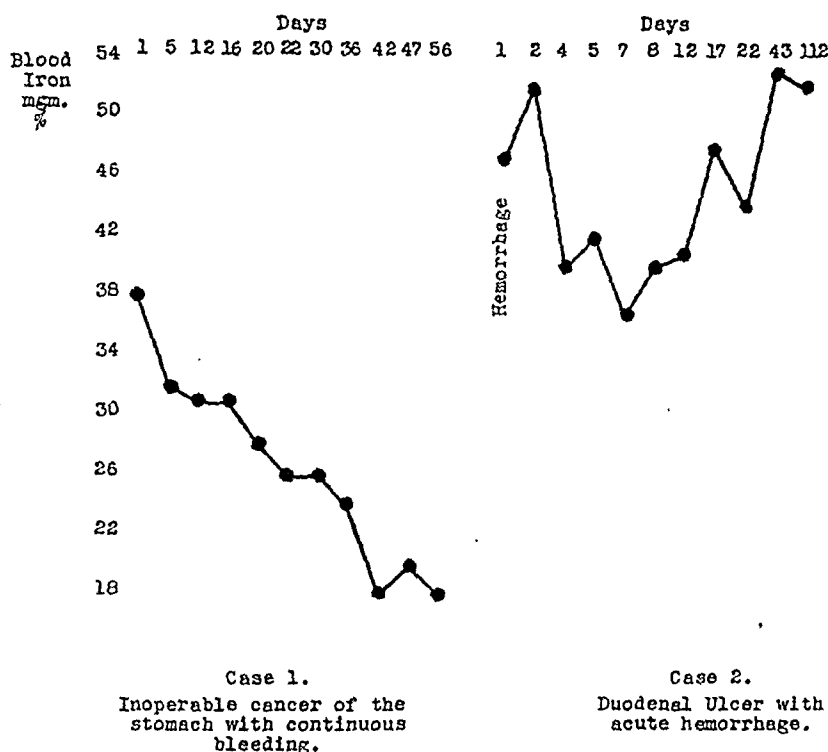


FIG. 3. The blood-iron level as affected by continuous bleeding and by acute hemorrhage.

measurement of hemoglobin in clinical laboratories are for the most part based upon the measurement of the color of acid hematin. Such methods are fundamentally inaccurate and subject to frequent inexplicable fluctuations as shown by Barkan<sup>9</sup> and others. The measurement of the total iron of the blood can be made, by the method described above or by several other methods, with analytical precision.

To return to our own cases. In the iron-poor group were examples of nearly all the clear-cut, well-established causes for depletion of hemoglobin. These included hemorrhage, pernicious anemia, myelophthisic anemia, aplasia of the bone marrow resulting from so-called idiopathic aplastic anemia, aplastic anemia following radiation in one patient who appeared hypersensitive to that form of therapy, and finally depletion of blood-iron and aplasia

3. A simple mechanical reason for this hypertension can be found in every case that can be adequately studied.

4. Hepatic cirrhosis exists in 68 per cent of our series as the obstructive factor. When cirrhosis is not present at the time of splenectomy it will not appear subsequently.

5. No clinical or hematological differences can be found between patients with congestive splenomegaly due to intra- or extrahepatic obstructions, except in cases of advanced liver disease when the clinical features of hepatic insufficiency will appear and assume preponderance.

6. The splenic histopathology is the same in all cases of congestive splenomegaly—it is similar in type to the changes described by Banti and others—there are no visible differences in the various groups.

It is, therefore, our present contention that Banti's disease or splenic anemia is a secondary mechanical manifestation of any of a variety of lesions producing a chronic splenic vein hypertension. We consider this syndrome as a mechanical congestive splenomegaly, a term suggested by Larrabee.<sup>15</sup>

In any given case the prognosis, with or without splenectomy, depends upon the nature and the location of the obstructive mechanism. In the extrahepatic group the cause of death is hemorrhage from ruptured esophageal varices. The majority of the intrahepatic group die of liver insufficiency, except in the pure periportal schistosomiasis cases, where death is from hemorrhage.

It is our experience and the experience of others that splenectomy is usually followed by a return of the blood values to normal. The threat of lethal hematemesis continues to be present in spite of splenectomy in those cases where the obstructive factor lies within the liver or in the portal vein. Splenectomy has no visible effect upon the progress of cirrhosis. But splenectomy should and, in our experience, does definitely cure that unfortunately small group where the splenic vein alone is involved.

#### CONCLUSIONS

1. Banti's disease or splenic anemia results from a variety of primary lesions that produce splenic vein hypertension.

2. We believe that this syndrome is a secondary mechanical congestive splenomegaly and we can find no reason for assuming the presence of an unknown toxic agent.

3. There is no justification for retaining the concept of three stages in development. In our experience cirrhosis of the liver exists only as one of the several obstructive mechanisms; if it is not present as the obstructive mechanism at the time of splenectomy, it will not develop subsequently.

4. We suggest that the terms Banti's disease and splenic anemia be replaced by congestive splenomegaly.

hemorrhage followed later by blood dilution and iron loss through bleeding, with final re-establishment of normal values. (Figure 4.)

One patient well illustrated the changes in blood-iron level which may occur from dilution of blood alone. The patient, a young man, was a diabetic. He developed an abscess of the lung following extraction of a

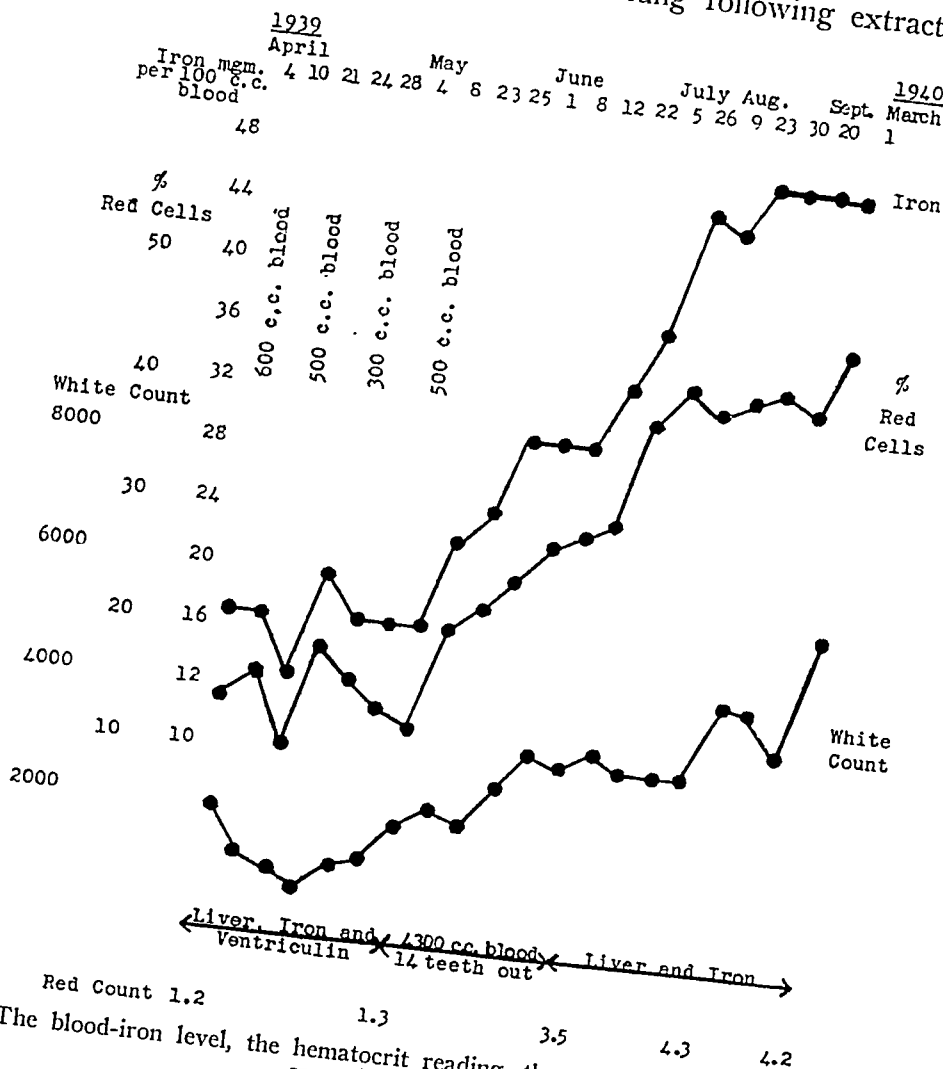


FIG. 5. The blood-iron level, the hematocrit reading, the white count and red count in a case of atypical anemia.

tooth and for this reason entered the Hospital. During the acute stage of this complication he received by vein large amounts of fluid. At first we did not realize how much fluid was being retained under such treatment and we were well on our way toward inducing a marked edema. Later by restricting the fluid intake a diuresis occurred with reconcentration of the blood. The various phases of dilution and concentration of the blood were well reflected by the blood-iron level.

It has been repeatedly emphasized that if the carriers of iron—the red discs—are at fault as in pernicious or aplastic anemia, treatment with iron

## CLINICAL OBSERVATIONS ON BLOOD IRON \*

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*Boston, Massachusetts*

THREE years ago at the Robert Dawson Evans Memorial, one of us (B. S. W.) adapted for determination of iron in whole blood the Wong<sup>1</sup> method using the photoelectric colorimeter of Evelyn.<sup>2</sup> Since then we have used this method almost as a routine in studying cases admitted to the hospital.

The following procedure is used: into a 100 c.c. volumetric flask the following are successively pipetted:

- 1 c.c. blood
- 4 c.c. concentrated sulfuric acid
- 4 c.c. saturated aqueous solution of potassium persulfate.

The mixture is shaken and allowed to cool. Distilled water is added until the flask is approximately half full, then 4 c.c. of 10 per cent aqueous solution of sodium tungstate, and finally distilled water to the 100 c.c. mark. After mixing and filtration, to 20 c.c. of the clear filtrate is added 1 c.c. of the persulfate solution and 4 c.c. of 3N potassium thiocyanate solution to which have been added 40 c.c. of acetone per liter of solution. This treatment of the filtrate with persulfate and thiocyanate is carried out in an Evelyn tube, the colorimetric reading being made promptly in the Evelyn instrument. The filter used transmits light at a wave length of 490 mμ; the maximal absorption of a solution of ferric thiocyanate is at a wave length of 480 mμ. Calculations are made from a curve obtained by actual determinations of galvanometer deflection with known iron solutions, or by the equation

$$\text{Mg. Fe per 100 c.c. blood} = \frac{(2 - \text{Log } G) \times 100}{K},$$

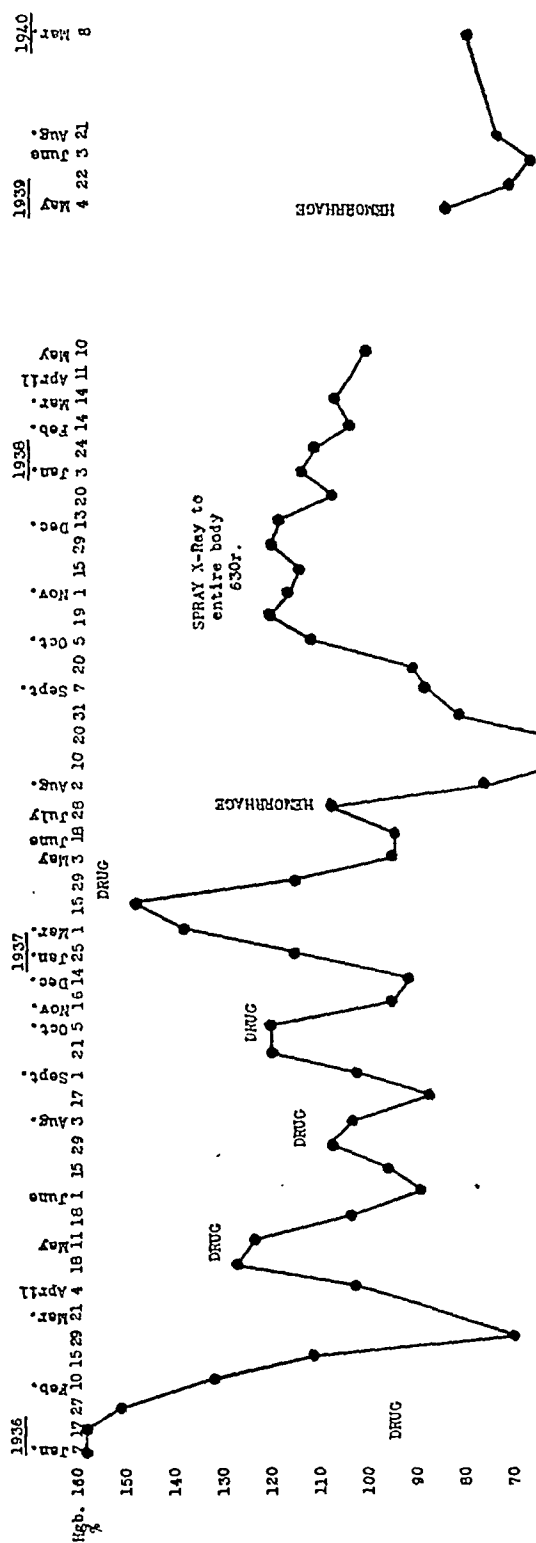
where  $G$  is the galvanometer deflection and  $K$  has the experimentally determined value of 2.44.

Up to July 13, 1939 the concentration of iron was determined in 2608 different samples of blood. When the data from these analyses were assembled, the blood-iron concentrations formed a frequency curve, the commonest blood-iron level being around 47, with a range between 8 and 86 mg. per 100 c.c.

To the best of our knowledge, this is the first tabulation of such a large series of blood-iron determinations. From so simple a statistical analysis it appears that by this method, and in this particular series, bloods containing less than 31 mg. of iron per 100 c.c. were unquestionably abnormal just as were bloods which contained more than 55 mg. per 100 c.c. As a whole, bloods with an iron concentration of less than 47 mg. per 100 c.c. were more

\* Read at the Cleveland meeting of the American College of Physicians, April 4, 1940.

From the Robert Dawson Evans Memorial for Clinical Research and Preventive Medicine, the Massachusetts Memorial Hospitals, Boston.



There were among the definitely abnormal bloods 257 samples (10 per cent of the series) which contained less than 31 mg. of iron per 100 c.c., and 138 samples (5 per cent of the series) which contained more than 55 mg. The iron-poor blood samples were obtained from 64 different cases and the iron-rich samples from 75 different cases. We determined to study the individual records of these cases in order to discover what circumstances are likely to lead to a significantly abnormal blood-iron level and whether information obtained from the blood-iron level is of any definite clinical interest.

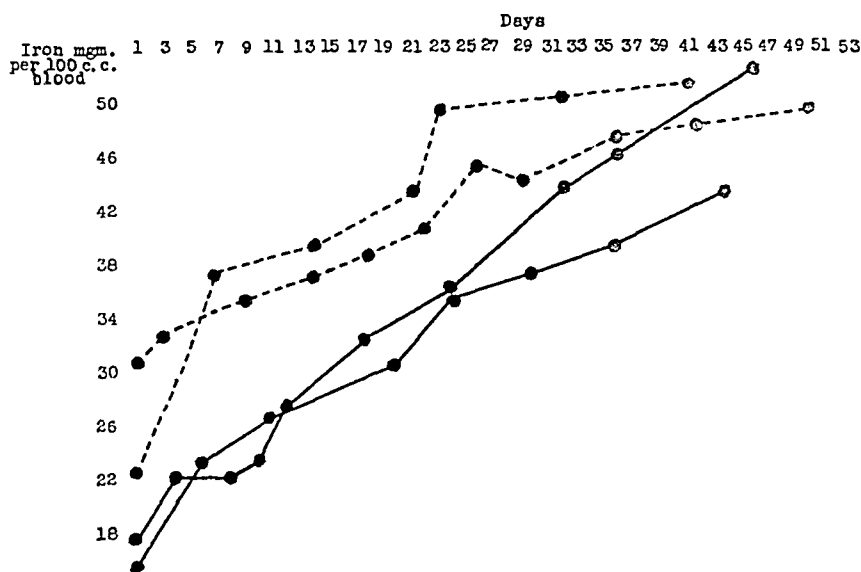


FIG. 2. The blood-iron level in two cases of pernicious anemia under treatment with liver and without iron, and in two cases of simple secondary anemia under treatment with iron and without liver. The pernicious anemia blood-iron curves are dotted. The secondary anemia blood-iron curves are solid.

Before considering any of the cases in detail, it may be well to recapitulate the present state of knowledge as to the forms of iron present in the blood and their distribution. Nearly all of the iron of the blood is in the red cells: plasma or serum contains normally about 0.1 mg. of iron per 100 c.c.,<sup>4</sup> or about 0.2 per cent of the total iron of the blood. In certain types of anemia<sup>4</sup> or following intensive iron therapy<sup>5</sup> the plasma or serum iron may be increased to several times this value. Considering both the possibility of an elevation of the serum iron and a depression of the total iron of the blood in anemias, the percentage of the total iron assignable to the plasma can in all reasonable probability surely never exceed 5 per cent. This leaves 95 per cent or more (usually 99 per cent or more) of the total iron of the blood to be accounted for in the corpuscles. The major portion of this iron is in the form of hemoglobin; a minor portion (not more than 10 per cent at the most, usually less than 5 per cent of the total iron) is present in the form of degradation products of hemoglobin in which the iron and globin are still in union with an *opened* porphyrin ring . . . the "pseudohemoglobins" of



planation of this case is correct, nor that the results of our treatment will be lasting. The explanation given is at least not altogether unreasonable.

Theoretically, significant degrees of anemia could develop in the presence of adequate iron storage and of normal facilities for iron transport if, through some form of abnormal metabolism, iron might not be made into hemoglobin at a normal rate. We have encountered a few cases of anemia in myxedema, for example, which did not initially respond to iron or liver or both. The anemia gradually corrected itself, sometimes without any accessory treatment, when the basal metabolic rate was maintained at a normal level over a long period of time by thyroid administration. It seems possible that faulty oxidation processes may have made the iron stores unavailable for hemoglobin synthesis. The effect of thyroid administration in stimulat-

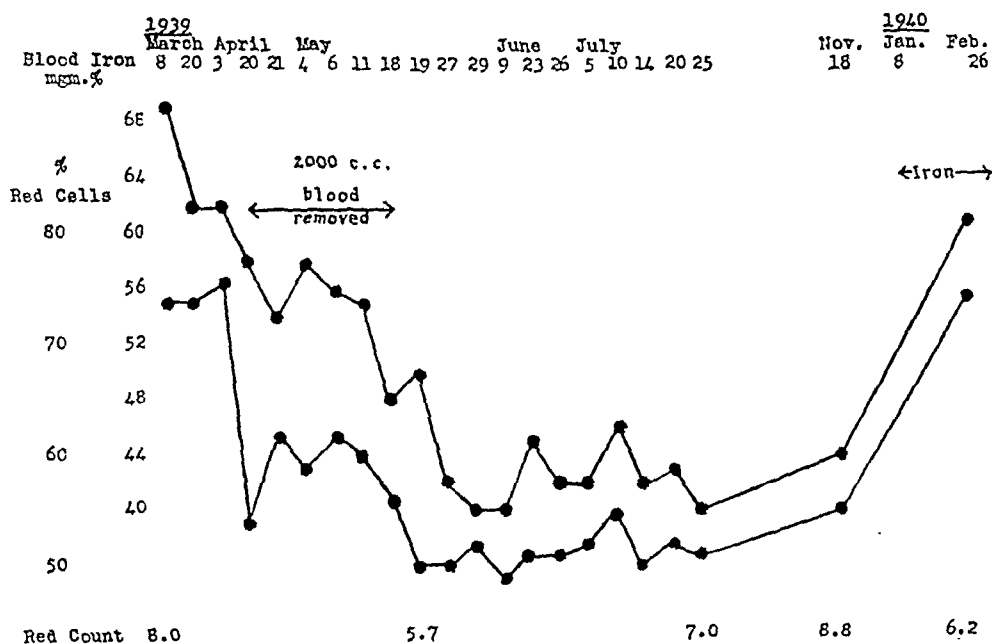


FIG. 9. The blood-iron level, the hematocrit reading and the red count in a case of secondary polycythemia treated by bleeding, and later by iron.

ing the formation of red discs even in non-myxedemic subjects has been reported by Hoskins and Sleeper.<sup>10</sup>

In light of these considerations we believe that a knowledge of the blood-iron level, in addition to its obvious function of serving as a check on hemoglobin estimations, affords information of definite value in the diagnosis and treatment of the several forms of anemia. It directs the attention of the clinician to the general state of the patient's iron metabolism, a matter which in the management of the anemias is not only of theoretical interest, but of very practical importance.

Certain of the patients with too high a level of blood-iron proved equally interesting. There were in the group four cases of polycythemia vera. Of these, three have been followed for a sufficiently long time to be worth dis-

of the marrow secondary to long-standing chronic infections or to chronic intoxication as occurs in cancer, advanced liver disease, or in chronic nephritis, particularly in chronic pyelonephritis. Hemorrhage, either acute or chronic, was the commonest single cause of an abnormally low blood-iron level.

Certain facts in these cases were outstanding. Too low a blood-iron level, for example, was an ominous sign. Of twelve cases in which the blood-iron level reached a point below 20 mg. per 100 c.c., nine died in a comparatively short time in spite of repeated transfusions or varying combinations of transfusions and liver or iron therapy.

The almost mathematical precision and parallel manner in which the level of blood-iron increased under appropriate treatment in cases with pernicious anemia receiving liver or in cases of anemia from hemorrhage receiving an adequate supply of iron was striking.

On the whole, the blood-iron level tended to be relatively high in severe pernicious anemia before treatment in contrast to its low level in severe un-

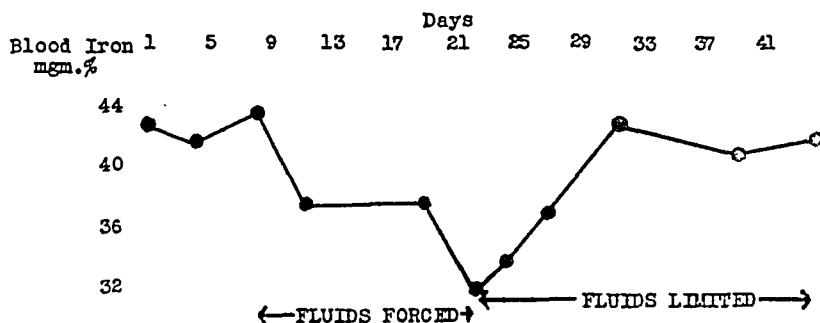


FIG. 4. The blood-iron level as affected by dilution from fluid retention.

treated hypochromic anemia. It often was easier to establish blood-iron levels higher than normal in pernicious anemia without the administration of iron than normal blood-iron levels in hypochromic anemia even with very high iron dosage. Obviously there is a striking difference between the iron metabolism of pernicious anemia on the one hand and that of hypochromic anemia on the other. In one condition iron is present in the body but cannot be used because of ineffective red corpuscle formation, and in the other iron is lacking or not usable in the body although normal iron carriers are available.

The response of the blood-iron to hemorrhage may be varied. We have noticed that following an acute, not excessive, intestinal hemorrhage there may at first appear an elevation in the blood-iron level followed later by a fall: whereas in persistent continuous loss of blood there is apt to be a steady decrease in blood-iron concentration. (Figure 3.)

In Case 1 there was continuous loss of blood each day and therefore a steady drain on the iron reserve with resultant depletion of stored iron. In Case 2 there was at first concentration of blood resulting from a sudden

five weeks. The patient very quickly grew to feel much better and reports that he has been in good health since his discharge from the hospital in July 1938. The immediate effect of such treatment on the blood-iron level was striking. (Figure 8.)

In the first case radiation appeared to succeed not only in destroying red cells but also in depleting iron storage. Since then, apparently, it has been impossible for the clinical manifestations of polycythemia to redevelop. It would seem improbable that the present low blood-iron level could be due to a continued effect of radiation lasting for more than two years since the last treatment.

The second case shows that phenylhydrazin had a notable effect in destroying red cells without, however, depleting iron storage. So it was that as soon as the drug was no longer administered the clinical manifestations of polycythemia reappeared. When the amount of stored iron was depleted by roentgen-ray and hemorrhage, however, the polycythemia seemed more permanently controlled.

In the third case five liters of blood, each containing approximately 700 mg. iron, were withdrawn deliberately. Thus the amount of iron in the body was depleted by about 3.5 gm. Should any of these patients again develop an abnormally high blood-iron level, how will they do it? If polycythemia vera is due primarily to disturbed iron metabolism, conceivably iron in a form not ordinarily used may be drawn upon and thus the blood-iron level may again become excessively high. On the other hand, if polycythemia vera is a true erythremia, there may develop an excessively high red count with a normal blood-iron level, the red cells produced being unable to get enough iron from iron storage to make their iron content normal. That a process of this nature may at times take place in polycythemia vera is suggested by a case which Dr. Marshall N. Fulton of Boston has had under observation for some time and has described to us. This patient, too, had been treated by repeated bleedings. His hemoglobin concentration has been kept within normal limits but his red count remains elevated: thus he has a persistent hypochromia, with excessive numbers of red cells.

There were two cases of polycythemia secondary to congenital heart disease. Clinically, both patients had the tetralogy of Fallot. One of these patients, a young woman 19 years old, had uncomfortable attacks of profound cyanosis. These were so frequent and disturbing that we decided to discover whether ablation of the polycythemia would make any difference to her subjective symptoms. Accordingly blood was withdrawn until the blood-iron level was brought to a point slightly below 47 mg. per cent.

Obviously a large quantity of iron was removed in 2000 c.c. of blood. We were able to reduce the blood-iron level to whatever point was selected. Withdrawal of the blood, however, had no particular effect on the patient's feelings nor did it have any demonstrable effect on the mechanics of her circulation.

Her blood behaved in an interesting fashion. Apparently the stimulation

at least at first, is not necessary or helpful. On the other hand, if the storage of iron in the body is depleted, iron in some form is chiefly required and devices to improve the transportation of iron are unlikely to be very helpful. It is probable that certain cases of anemia result from a two-fold mechanism due to a combination of depleted iron stores and faulty iron transportation. A patient with an atypical anemia associated with splenomegaly, leukopenia and a tendency to bleeding gums perhaps fell into this category.

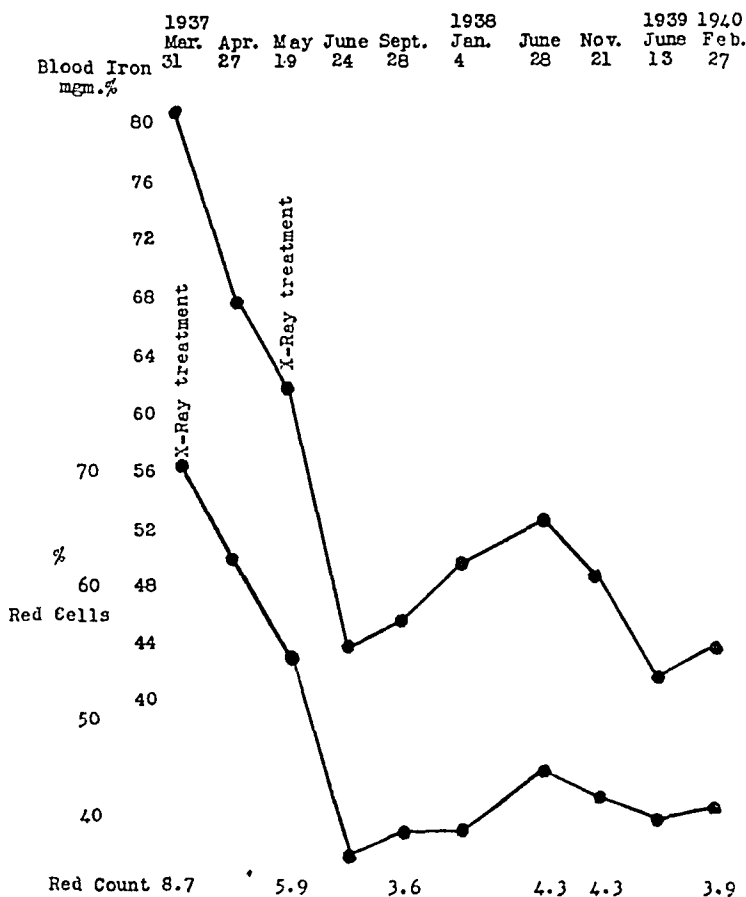


FIG. 6. The blood-iron level, the hematocrit reading and the red count in a case of polycythemia vera treated by radiation.

At first liver, stomach and iron therapy were without demonstrable effect. It was thought that the patient had aplastic anemia. Multiple transfusions were then given, 500 c.c. every three days for several weeks. During this period several badly infected teeth were removed. Finally the patient was given a diet high in vitamins, supplemented by liver and iron. Now there developed a slight reticulocytosis (3 per cent) which had not been heretofore obtained and steady improvement. (Figure 5.)

Apparently this patient had depleted iron storage: our reason for believing this was the low blood-iron level first encountered which was lower than

A knowledge of the blood-iron level is proving, in our experience, of considerable practical interest.

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is usual in pernicious anemia. In addition to persistent bleeding, another factor in depleting the iron storage may have been a diminution of hydrochloric acid in the gastric juice and therefore she may have absorbed iron with difficulty. And finally, possibly as a result of infection, the bone mar-

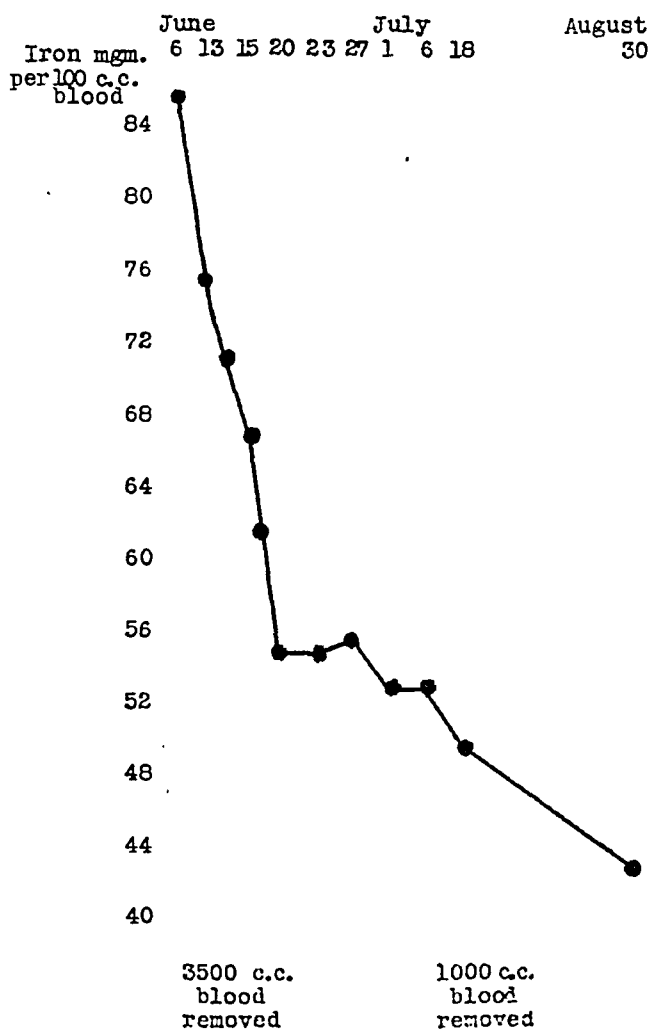


FIG. 8. The blood-iron level in a case of polycythemia vera treated by copious bleeding.

row had become relatively aplastic and therefore the iron transport was abnormal.

Transfusion supplied iron, for normal blood appears to afford the most satisfactory method at present available for the parenteral administration of iron. Five liters of blood, containing (approximately) 470 mg. of iron per liter, supplied in a short time more than 2 grams of iron. The removal of infected teeth did away with a possible cause of bone marrow aplasia. When the iron storage approached adequacy and the marrow was no longer aplastic, improvement became possible. We are by no means certain that our ex-

from two months to 10 years. One hundred and twenty-four patients had no previous treatment, 19 were in remission, and 57 were in relapse. The red blood cell counts varied from 500,000 to 5,000,000 per cubic millimeter.

Of the 200 cases reviewed, there were six (3 per cent) in whom the spleen was palpable. More complete and specific data concerning these six cases are contained in the table. The red blood cell measurements of these individuals differed from those of the others in the series in that the diameters of the majority of the cells were less than 7.5 microns. Examining the stained cells, it was noted that the largest percentage of them were small in diameter, but were spherical in appearance. In one case (B. V.) in which the cells were tested, their resistance to hypotonic salt solution was less than normal.

In a total of 18 autopsies the weight of the spleen varied from 95 grams to 640 grams, the average being 265 grams. In 17 of the autopsies performed the spleen was larger than the normal weight of 150 grams, although but one was palpable. This value for "normal" was obtained from Krumbhaar and Lippincott's<sup>5</sup> recent study of a series of 4,000 postmortem examinations in traumatic deaths and diseases not associated with splenomegaly. An autopsy was carried out in only one individual in whom the spleen was palpable. A summary of this case follows:

#### CASE REPORT

The patient was a 54 year old white male who was admitted complaining of weakness, tiring easily, pallor, dyspnea, and palpitation of the heart on mild exertion. These symptoms had been present for six months. His appetite had been poor, and there had been a weight loss of 50 pounds. Soreness of the tongue had never been noticed. There were no paresthesias.

Physical examination: The essential features were pallor of the skin and mucous membranes, gray hair, blue irides, dyspnea at rest. The heart was moderately enlarged, with loud hemic murmurs at the apex and base. Blood pressure was 150 systolic and 80 diastolic. Transitory coarse râles were heard at both lung bases. The tongue showed early atrophy of the papillae. The liver edge was palpable just below the right costal margin. The spleen was palpable five centimeters below the left costal margin; it was firm and not tender. There was moderate pitting edema of the lower extremities. Neurological examination was negative.

Examination of the blood: Red blood cells 760,000 per cu. mm.; hemoglobin 18 per cent (S); white blood cells 6,350 per cu. mm.; polymorphonuclear neutrophils 68 per cent; lymphocytes 27 per cent; monocytes 3 per cent; eosinophiles 1 per cent. There were many immature red blood cells with nucleated forms and occasional poikilocytes. Red blood cell measurements: 45 per cent of the red blood cells were smaller than 7.5 microns; 33 per cent were 7.5 microns; and 22 per cent were larger than 7.5 microns. Gastric analysis was not done because of the poor condition of the patient.

The patient was digitalized immediately, given transfusions and intravenous liver extract. There was a reticulocyte response to 34.5 per cent on the seventh day of treatment. He ran a progressively downhill course, however, and died on his eighth hospital day. The significant autopsy findings were congestive heart failure, hyperplasia of the bone marrow, and well advanced atrophic cirrhosis. The spleen weighed 640 grams.

cussing from the viewpoint of iron metabolism, particularly because each one has been treated in different fashion.

The first patient, a man of 55, developed polycythemia in 1935. He had all the earmarks of the disease including an excessively high hemoglobin concentration, a red count of more than eight million and a palpable spleen. At first he was given large doses of Fowler's solution with subjective benefit. But the drug, to be effective, had to be given in uncomfortably large quantity so that in 1937 a more radical treatment was attempted. He was given two courses of roentgen-ray treatment by Dr. George W. Holmes at the Massachusetts General Hospital. Observations on the blood-iron level have been made from time to time since then with the results shown in figure 6.

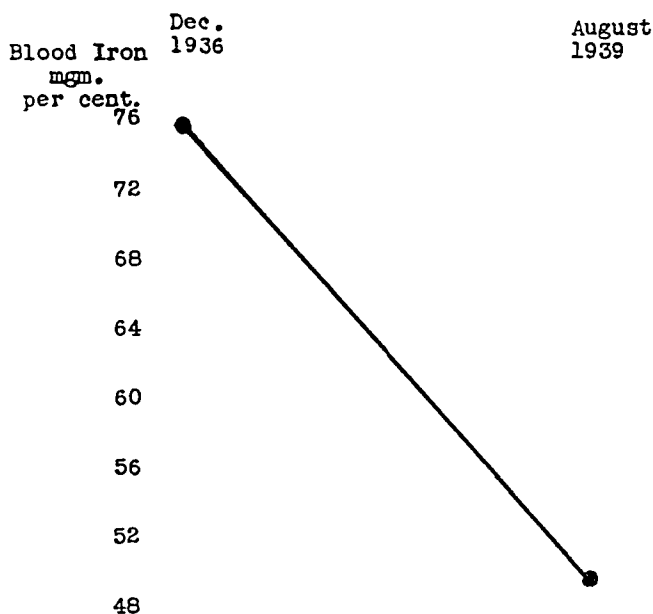


FIG. 10. The blood-iron level in a case of secondary polycythemia receiving no therapy.

The second case, a woman of 56, was found to have polycythemia four years ago. She was treated with acetylphenylhydrazin under the direction of Dr. Helmuth Ulrich.\* In July 1937, however, she had a large gastrointestinal hemorrhage and this was repeated in 1939. Since December 1937 she has had no treatment of polycythemia. (Figure 7.)

The third case, a man 58 years old, entered the Robert Dawson Evans Memorial in June 1938. He had cerebral thrombosis as a complication of polycythemia vera when he first was seen. The hemoglobin concentration was around 160 per cent, and the red count over seven million. It was decided to treat this patient by the method of bleeding alone. Repeated bleedings of 1000 c.c. each were made at frequent intervals until the blood-iron level was reduced to a figure within normal limits. In order to accomplish this purpose, five liters of blood were withdrawn within a period of

\* We wish to thank Dr. Ulrich for allowing us to report the case and to use these data.



5. The presence of a palpable spleen in a patient suspected of having pernicious anemia is of such rarity that it suggests the possibility either of some complication or of some other disease.

TABLE I  
Data on the 6 Cases in This Series in Which the Spleen Was Palpable

Patient	Sex	Age	Status	Duration of Symptoms	R.B.C. Millions per cu. mm.	Lower Edge of Spleen	Complications
M. B.	F	46	Untreated	1½ yrs.	0.97	5 cm. below L.C.M.	Cholecystitis with cholelithiasis
A. B.	F	51	Relapse	2 yrs.	0.5	3 cm. below L.C.M.	Spleen no longer palpable after institution of treatment
A. T.	M	54	Untreated	6 mos.	0.79	5 cm. below L.C.M.	Congestive heart failure; cirrhosis of liver
B. V.	F	57	Relapse	5 yrs.	1.1	4 cm. below L.C.M.	Marked congestive heart failure; hypertensive heart disease
E. P.	M	40	Relapse	1½ yrs.	1.4	7 cm. below L.C.M.	Congestive heart failure
M. F.	F	33	Untreated	2 yrs.	1.8	3 cm. below L.C.M.	None

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of chronic cyanosis and anoxemia activated her bone marrow so that the red count rose from a low point of 5.7 million to 8.8 million. There being no iron available, however, she developed a profound hypochromic anemia despite the abnormally elevated red count. Finally she was given iron and as a result the blood-iron level increased, the red count fell, she re-developed a polycythemic hematocrit reading and was brought back to much the same stage she was in before bleeding was undertaken. (Figure 9.)

The second case, another young woman, was under observation in 1936 and again in 1939. Between these two periods there had been no therapy. The blood-iron level behaved most remarkably during this interim. (Figure 10.)

Apparently this patient's blood-iron plethora has largely disappeared. No appreciable change in the heart condition has taken place and the mechanics of the circulation are unchanged. There is no history of blood loss. Is it possible that the high blood-iron level has disappeared and readjustments have been made because there no longer is iron enough available in storage to maintain so high a level?

The iron plethora of polycythemia may now be treated with success in various ways. But the fact of the matter is that very little is known of the essential nature of the condition.

The remainder of the cases with an abnormally high level of blood-iron were an odd lot difficult to classify satisfactorily. A certain number were patients who were moderately dehydrated at entry to the hospital and after rest in bed with adequate fluid intake their blood-iron values promptly fell to normal. Others, particularly a group of middle-aged rather stout men with moderate hypertension seemed to be full-blooded individuals without showing any particular reason for thinking that their full-bloodedness was of clinical significance. A few, strangely enough, were anemic patients, particularly with pernicious anemia, who under treatment seemed to over-correct and developed for varying lengths of time iron plethora. A certain number of cardiacs in decompensation had abnormally high blood-iron levels which became normal as cardiac compensation was regained. Thus there seem to be several factors which may lead temporarily to an abnormally high blood-iron level. Out of the hodge-podge of our material, however, the cases of polycythemia vera and of marked secondary polycythemia were the striking ones. The other cases were too indefinite to be worth more than very brief mention.

In summary, we believe that a knowledge of the blood-iron level is of clinical usefulness. The blood-iron level indicates by an accurate chemical method the hemoglobin concentration of the circulating blood and also gives indirect evidence concerning the amount of iron stored within the body.\* The factors of storage of iron and transport of iron are each of importance in the accurate diagnosis and treatment of patients with anemia or polycythemia.

\* Direct evidence as to the amount of iron available for hemoglobin production is given by the measurement of serum iron, the level of which must necessarily be interpreted in terms of the total blood-iron. The significance of serum iron estimations has already been discussed by one of us,<sup>4</sup> and this portion of the study of iron metabolism has been purposely omitted from this paper for considerations of unity and brevity.

do not lend themselves to quantitative determinations and are not adaptable to measure rapid fluctuations which may occur.

In this study artificial fever was induced by means of the Kettering hypertherm, a sealed air conditioned box in which the patient's body, except the head, lies entirely free on a rubber air mattress. Stecher and Solomon<sup>8</sup>

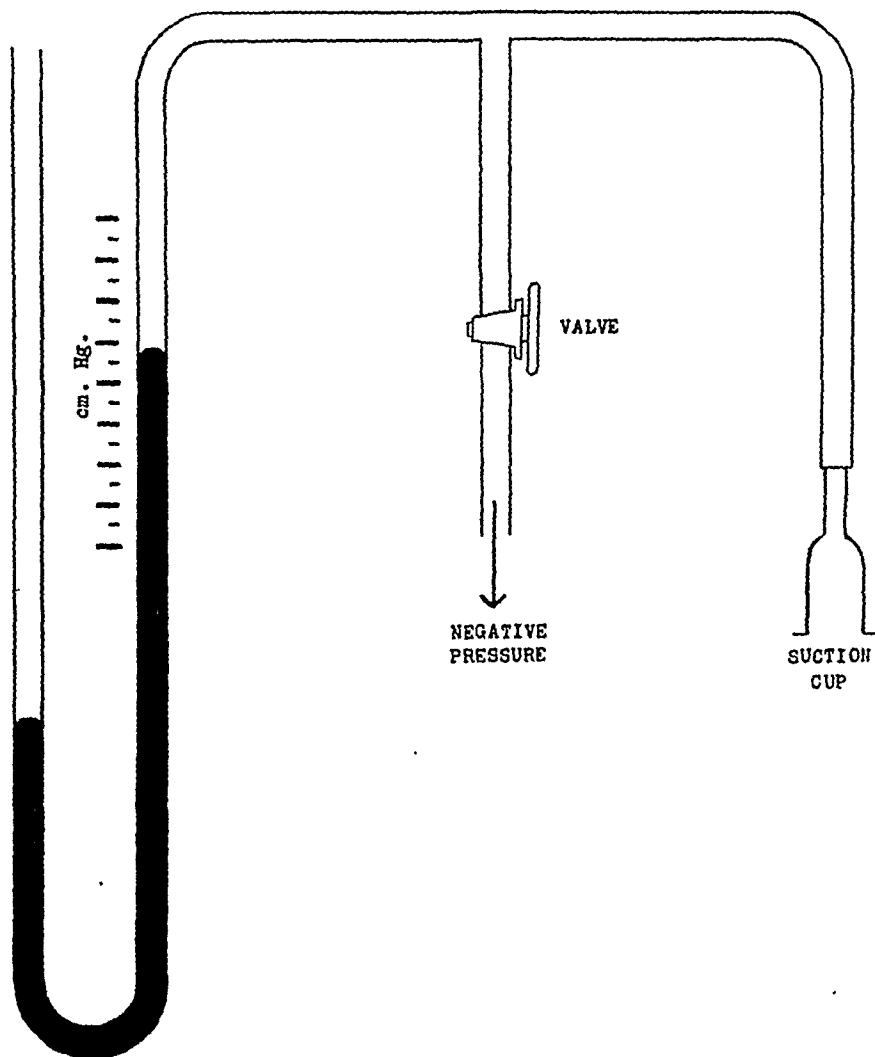


FIG. 1. Schematic diagram of apparatus used to determine capillary resistance.

give a more detailed description of the procedure followed. The suction cup was applied to the patient's forearm through a partially opened panel door of the fever chamber. Opening this door usually caused the temperature of the cabinet to fall from two to five degrees (F.), but the loss was quickly restored when the door was closed.

Observations were made on 12 patients, seven males and five females, whose ages ranged from 8 to 53 years. They had the following diseases: atrophic arthritis, gonorrheal arthritis, gonorrheal urethritis, ankylosing

# SPLEEN SIZE IN PERNICIOUS ANEMIA \*

By EDWARD BIGG, M.D., *Chicago, Illinois*

A PALPABLE spleen has long been accepted as an expected finding in the physical examination of a patient suffering from pernicious anemia. Although Sturgis<sup>11</sup> reported the spleen to be rarely palpable and Minot<sup>7</sup> pointed out that it was palpable in only 5 per cent of his cases, the majority of standard textbooks and monographs on pernicious anemia give the incidence as from 20 to 50 per cent.

Evans<sup>3</sup> reported the spleen to be palpable in 20 per cent of his cases. In McCarty's<sup>6</sup> series of 51 cases the spleen was palpably enlarged in 45 per cent. Cornell<sup>2</sup> stated that the "spleen is not infrequently enlarged," and points out that this enlargement is important in the differential diagnosis, as it may confuse the disease with endocarditis, leukemia, polycythemia, and Gaucher's disease. Stevens<sup>10</sup> noted that slight or moderate enlargement of the spleen is frequently observed, and that occasionally the organ may extend almost to the level of the umbilicus. Wintrobe and Musser<sup>13</sup> reported that the spleen is moderately increased in size in 40 per cent of cases and palpable in 25 per cent. Ordway and Gorham<sup>9</sup> found that in one-third to one-half of their cases it is palpable and occasionally markedly enlarged. Kracke and Garver<sup>4</sup> mentioned that the spleen may be enlarged sufficiently so that it may be palpated in less than one-half of the cases. Meakins<sup>8</sup> reported that in 30 per cent of the cases the spleen is definitely palpable. Suarez<sup>12</sup> used the presence of a palpable spleen as a diagnostic aid in differentiating pernicious anemia from tropical sprue.

## MATERIALS AND METHODS

The material used for this report is based on the records of patients seen and treated at the Simpson Memorial Institute for Medical Research. Two hundred consecutive case records were reviewed. Each of these patients has been examined by at least six different physicians, each of whom recorded his findings independently. The diagnosis of pernicious anemia was established by complete histories, physical examinations, and laboratory studies. All cases showed the expected response to specific anti-pernicious anemia therapy. A total of 18 autopsies was done; only one of the patients with a palpable spleen had a postmortem examination.

## DATA

One hundred and ten cases examined were males, and 90 were females. The ages varied from 21 to 80. The duration of the symptoms ranged

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From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan.

during the recession of fever. Figure 3 shows representative temperature and capillary resistance curves during a typical fever treatment.

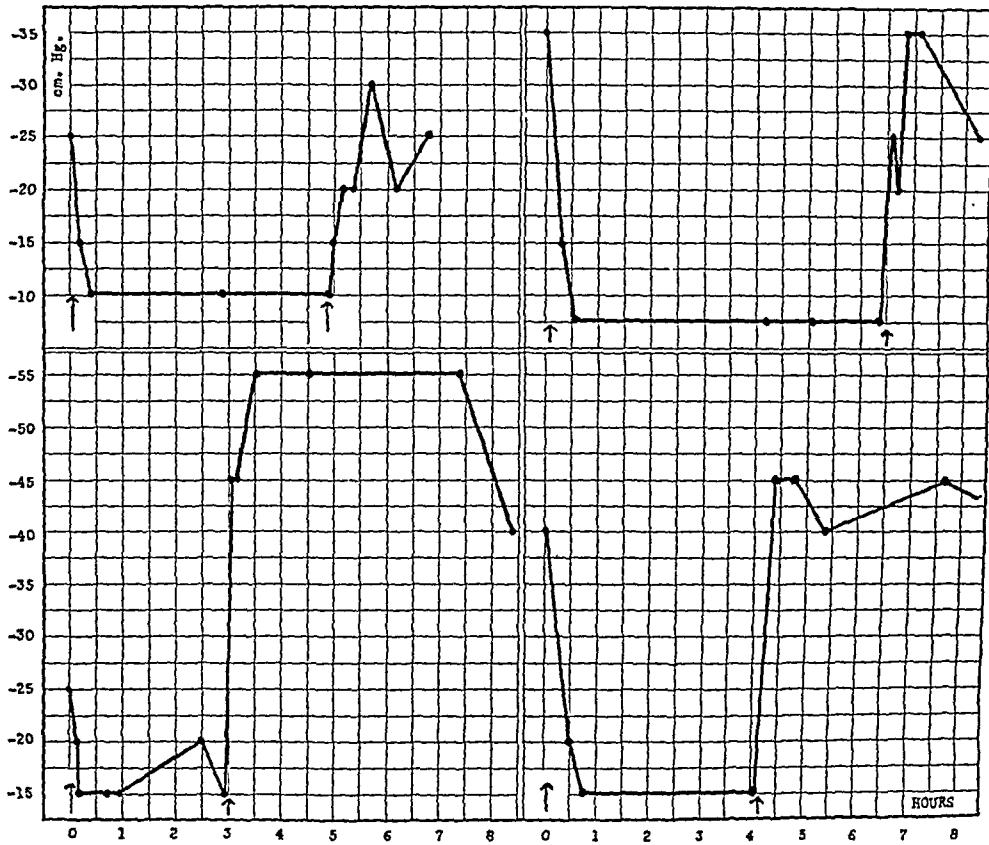


FIG. 2. Capillary resistance in four patients during artificially induced fever. The arrows denote the beginning and end of the treatments.

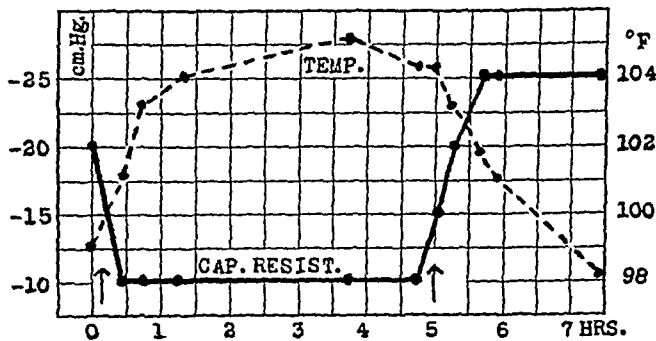


FIG. 3. Rectal temperature and capillary resistance during an artificially induced fever treatment. The arrows denote the beginning and end of the treatment.

Observations on three patients were repeated at a later date. The second curves were similar but not exactly comparable to the initial ones.

Other studies on the localized application of heat to one arm by means of a heat lamp or by inserting one arm in a fever cabinet also showed a re-

## DISCUSSION

Unfortunately there were no data on the cell volume of these patients. However, of another group of patients, one with a large spleen showed small red blood cells as in these cases, but the mean corpuscular volume was larger. From this it is surmised that the red blood cell volume in the six cases herein described was also larger, as the cells had the appearance of spherical cells in the stained preparations. In five of the cases complications such as cholecystitis, cholelithiasis, cirrhosis of the liver or congestive heart failure were contributing causes of splenomegaly. In one case no evident accessory cause for a palpable spleen was apparent.

During the past decade great advances have been made in our concept of anemias. There can be little doubt that many cases of macrocytic anemia which were formerly classified as pernicious anemia are today recognized as different entities. The macrocytic anemias associated with pregnancy, food deficiency, fish tapeworm, myxedema, carcinoma of the stomach and cirrhosis of the liver are examples of such previous erroneous diagnoses. The case reported above illustrates the difficulty in differentiating the last named condition from pernicious anemia. Although it cannot be said that the five other cases with enlarged spleen also had cirrhosis of the liver, it is of interest to note that the stained blood preparations deviated from the classical expected finding.

It appears that the incidence of a palpable spleen is definitely less than has heretofore been believed. It further appears that this decrease is more likely dependent upon more exact methods of diagnosis and more thorough understanding of the disease, rather than upon the institution of specific therapy as suggested by Minot.<sup>7</sup> The presence of a palpable spleen is of such rarity that if it occurs in a patient suspected of having pernicious anemia it suggests the possibility either of a complication or of another disease.

Most of the spleens examined at autopsy were larger than normal. It is evident that a spleen may be increased 400 per cent in weight without being palpable. In Askanazy's<sup>1</sup> summary of spleen weights in 461 cases of pernicious anemia, reported from different parts of the world, 321 (69.6 per cent) had spleens weighing over 150 grams. The largest weighed 1200 grams. Causes for splenomegaly in this series were given as active and passive hyperemia, hyperplasia, hematopoiesis, and occasionally infection.

## CONCLUSIONS

1. In a series of 200 consecutive cases of pernicious anemia the spleen could be palpated in 3 per cent.
2. The red blood cells in these six individuals were presumably spherical.
3. One patient was proved at autopsy to have cirrhosis of the liver.
4. In 18 cases which came to autopsy, there was some degree of enlargement of the spleen in 94.6 per cent. In only one of these cases was the spleen palpable.

ciated with obstructive jaundice was due to a low plasma prothrombin. The prothrombin level was restored and bleeding successfully controlled by the use of vitamin K and bile salts.<sup>16</sup> The use of these substances as a prophylactic measure may be indicated in therapeutic hyperthermia in view of the low plasma prothrombin which occurs.

The lowered capillary resistance only at the site of application of heat demonstrates that the phenomenon does not depend on systemic changes and can be purely a local reaction.

Changes in peripheral and visceral capillary resistance during artificially induced fever are probably not concomitant. According to Bazett,<sup>17</sup> exposure of the body to heat causes an increase in the blood volume of the skin due to the dilatation of arterioles, capillaries and veins. At the same time there is a compensatory constriction in the central vessels, particularly in the splanchnic area, so that, with the more or less maintained peripheral resistance and volume of the vascular bed, there is only slight diminution, if any, in cardiac output and blood pressure. An increase in blood volume is the alternative adjustment mechanism to compensatory vasoconstriction. Bazett<sup>17</sup> showed that this may occur with exposure to heat prolonged for a period of days, but no valid evidence has been advanced of acute increases in blood volume exceeding 10 per cent of the normal value for short exposures.

If the tendency to hemorrhage in visceral organs is dependent at all upon capillary resistance, then this tendency is probably greatest when the patient is removed from the fever cabinet at the end of the treatment. At this time the skin capillaries become highly resistant, presumably due to a central shift in blood distribution as a result of peripheral vasoconstriction and visceral vasodilatation. Further investigation may show that it is best to reduce cabinet heat slowly at the end of a treatment instead of suddenly taking the patient out of the fever cabinet and causing a rush of blood from the periphery to the visceral organs.

#### SUMMARY

1. Artificial fever, induced by means of the Kettering hypertherm, produced an immediate decrease in capillary resistance as determined by the suction test applied to the skin of the forearm.

2. A quick return of the skin capillaries to normal resistance, with a temporary hyperresistance in many instances, occurred following a fever treatment.

3. The focal hemorrhages seen at autopsy following artificially induced fever in experimental and clinical subjects may be due to decreased capillary resistance.

4. The exact cause of this decreased capillary resistance is as yet unknown. Vasodilatation and increased intracapillary pressure are probably the underlying factors.

The author wishes to express his appreciation to Dr. R. M. Stecher and his staff for their helpful cooperation, and to Dr. J. L. Work for his study of the biopsy specimens.

# CAPILLARY RESISTANCE IN ARTIFICIALLY INDUCED FEVER\*

By PHILLIP L. ROSSMAN, M.D., *Cleveland, Ohio*

IN an attempt to explain the mechanism of hemorrhage in artificially induced fever, studies of capillary resistance by means of the suction test were made on 12 subjects, three of whom were used twice, making a total of 15 observations.

The outstanding pathologic observations in experimental animals and human subjects following induced fever have been the presence at autopsy of focal hemorrhages and acute parenchymatous degeneration of the organs. Giles, Harvey and Dampere,<sup>1</sup> in a study of the effect of exogenous heat on rabbits, saw marked focal hemorrhages in the viscera and central nervous system on examination of the non-surviving animals. Hyperemia and cloudy swelling of the organs, as well as degenerating lesions in the male generative epithelium, were noted. In a study of two human beings and 20 experimental animals under accurately controlled fever conditions, Hartman and Major<sup>2</sup> described pathologic changes consisting of engorgement of blood vessels, especially of capillaries, hemorrhage and degeneration of the adrenal cortex, hemorrhages in the brain, edema and congestion of the lungs, and parenchymatous degeneration of the liver and kidneys. Schnabel and Fetter,<sup>3</sup> Watts and Hartman,<sup>4</sup> and Wilbur and Stevens<sup>5</sup> report similar observations.

## METHOD

The suction test consists in the application of a small cup with an inside diameter of 1 cm. to the volar surface of the forearm just below the antecubital fossa. A negative pressure is then maintained for one minute at a given level as determined by a mercury or aneroid manometer (figure 1). The capillary resistance is considered to be the lowest negative pressure required to produce at least two macroscopic petechiae. This test is probably the simplest and most accurate method of measuring frequent fluctuations in capillary resistance. It was first described by Hecht<sup>6</sup> in 1907, and has been used widely in the study of scurvy and hemorrhagic diseases.

Dalldorf<sup>7</sup> and others have pointed out inherent weaknesses in the suction test. There are many variables such as thickness, texture and color of the skin even in the same individual. Spontaneous hemorrhages may occur, necessitating examination of the skin before the suction cup is applied. Petechiae are difficult to see in negroes due to the skin pigmentation. The tourniquet test, flicking test, and intradermal venom test are also used to study capillary resistance, but they have further disadvantages in that they

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# THE TREATMENT OF HYPERTENSION; MEDICAL VERSUS SURGICAL \*

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THE title of our presentation was not intended to imply a conflict between the medical and the surgical treatment of hypertension. Rather, it was worded to express an attempt to evaluate the respective merits of these two methods of treatment. As internist and neurosurgeon, our primary interest in hypertension and that of our clinical associates is a therapeutic one; we want to find out what can be done to relieve hypertension and the symptoms which it produces. This report is of a continuation of studies reported earlier.<sup>1-7</sup>

The importance of hypertension as a problem of health needs emphasis. High blood pressure is both a common disease and a serious one. Indeed, it appears to be more common and more deadly than cancer. At The Mayo Clinic, each year, we encounter from five to six thousand patients who have definite hypertension. Cardiovascular-renal disease kills 500,000 people annually in the United States; that is, it kills four times as many people as cancer does. Apparently, hypertension accounts for from a half to three-fourths of all deaths referable to cardiovascular-renal disease, and thus is from two to three times as deadly as cancer.<sup>8, 9</sup> † About a fourth of all deaths of individuals past 50 years of life is referable to hypertension.<sup>10</sup> Keith, Wagener and Barker have shown that the mortality in hypertension,<sup>11</sup> groups 1 and 2, is 30 and 42 per cent, respectively, in four years from the time of their diagnosis; whereas, for a similar period, the mortality of hypertension, group 3, is 78 per cent and in group 4, it is 98 per cent.<sup>11</sup> Among subjects who have systolic blood pressures of about 170 mm. of mercury, the relation of actual mortality to expected mortality according to insurance statistics is as 219.6 to 100; among those patients whose systolic blood pressures exceed 200 mm. of mercury the actual mortality is to the expected as 827.5 is to 100.<sup>10, 12</sup> For individuals more than 40 years of age, systolic blood pressure ranging from 35 to 44 mm. in excess of normal increases the expected mortality two and a half times. Such a slight increase in blood pressure as that represented by the figures 170 to 174, systolic, and 106, diastolic, expressed in millimeters of mercury, increases the expected mortality two and a half times.<sup>13</sup>

Many physicians appear to be misled by the observation that an occasional patient survives hypertension for many years. They may then believe that

\* Read before the meeting of the American College of Physicians, Cleveland, Ohio, April 2, 1940.

† On this basis, the estimated mortality from hypertension would be 250,000 to 375,000 deaths annually in the United States. Another author estimated in 1924 that 140,000 deaths were caused annually by hypertension.

spondylitis, general paresis, rheumatic heart disease, chorea, and chronic ulcerative colitis. The patients were in the cabinets from three to six and a half hours. No attempt was made to correlate such related factors as skin temperature, blood pressure, platelet and blood counts, prothrombin and fibrinogen determinations, bleeding and clotting times, blood oxygen and carbon dioxide determinations, etc. Rectal temperatures were recorded by means of a mercury thermometer at each reading of capillary resistance.

## RESULTS

Control readings taken before the patients were placed in the fever cabinets varied from 20 to 40 cm. of mercury negative pressure. These were within the normal range obtained by Dalldorf<sup>7</sup> and others. At time intervals varying from two to 20 minutes after the patient was placed in the fever cabinet there occurred in all instances an increase in the ease of producing capillary hemorrhage. Negative pressure readings fell from 5 to 30 cm. of mercury. To obtain the rate of fall, readings were taken every few minutes after the patient was placed in the hypertherm. The exact rate of change could not be determined in most instances, because time was frequently lost in making the trial determinations necessary to get the lowest negative pressure which would produce at least two petechiae. The initial drop was usually greatest when the control reading was high. The lowest resistance obtained was 7.5 cm. of mercury. In 11 out of 15 observations readings were reduced to either 10 or 15 cm., definitely abnormally low results as compared to normal standards.

In seven instances capillary resistance remained at a constant low level during the entire treatment. The other eight showed a fluctuation of 5 to 10 cm. In the former group there may have been fluctuations which occurred during a non-observation period. Spontaneous hemorrhages of the skin were not observed at any time. The patients perspired freely during the treatments.

A rapid decrease in the ease of producing petechiae occurred when the patients were removed from the hypertherm. This was noted regardless of the duration of the treatment. Readings rose to a minimum of 25 and a maximum of 65 cm. of mercury usually within a period of a few minutes. In 13 of the 15 records the post-treatment increase in capillary resistance exceeded the initial control reading by 5 to 40 cm. of mercury. The remaining two records showed a return to the same level as the control.

At intervals of two to eight hours after the treatments seven readings were above, three were below and five were the same as the control readings. Most of the experiments were terminated after a total of eight hours. Figure 2 shows four records of capillary resistance obtained during fever treatments.

There was no quantitative correlation of body temperature (rectal) and capillary resistance. A given body temperature during the onset of fever did not produce the same capillary resistance as did that same temperature

## MEDICAL TREATMENT

Since hypertension is produced by increased resistance offered to the flow of blood through the arterioles, the specific need in medical treatment is a preparation which will restore arteriolar resistance to normal and which will not produce harmful or unpleasant side effects. Unfortunately, such a preparation is not available now.

It is well to state herein that the belief which persists stubbornly that it is inadvisable to lower blood pressure in the presence of essential hypertension has no foundation in fact. Vital functions continue normally when blood pressure is reduced and we doubt that reduction of blood pressure in itself is ever harmful. We believe that such a reduction is highly desirable in hypertension. Many drugs have been recommended for the treatment of hypertension. The very number of them convicts them of comparative or actual uselessness. There is surprisingly little evidence in the medical literature to indicate that many of the remedies so enthusiastically advertised have virtues. Over a period of years we have tried many of them without being convinced that they have any specific effect on blood pressure.

It has been shown repeatedly that blood pressure is not static but is labile. This is particularly true in the presence of hypertension, when the blood pressure fluctuates greatly.<sup>15, 16</sup> We have shown that if the systolic blood pressures of a group of patients in the clinic were more than 200 mm. of mercury, subsequent readings in the hospital would show that the systolic blood pressure decreased an average of about 50 mm. of mercury and that the average for the diastolic blood pressure decreased about 35 mm. of mercury, when no specific treatment was administered.<sup>17</sup> If all physicians who wrote of reduction of blood pressure as resulting from some specific method of treatment would determine the blood pressure of their patients hourly for 24 consecutive hours, they would not err in attributing to some specific method of treatment those reductions in blood pressure which occur without specific treatment. There can be but little doubt that the popularity of many remedies is based on observation of diminution of blood pressure; a diminution which has occurred spontaneously and has not resulted from a specific remedy.

The nitrites, purine derivatives (for example, theobromine and theophylline), iodides and extracts of tissue are probably of little or no value in the treatment of hypertension.<sup>10</sup> Too frequently a remedy achieves popularity because of its supposed beneficial effects which are found to be absent when careful studies are carried out. Such is the case of bismuth subnitrate.<sup>18, 19</sup> Occasionally, when hypertension develops during the menopause, there may be reduction of it as a result of the administration of ovarian follicular hormone or placental hormone. However, it is inadvisable to continue to treat such patients over long periods with these hormones for the purpose of reducing the blood pressure unless a definite reduction of the blood pressure can be shown to follow adequate dosage

duction in capillary resistance and a period of hyperresistance after the heat was removed. The opposite arm, used as a control, showed no change. Two patients with neurosyphilis who were inoculated with tertian malaria, and two others who were given fever treatments by means of typhoid-paratyphoid vaccine, showed similar changes in capillary resistance during the febrile period, but to a lesser degree.

To study the histologic structure of petechiae produced by means of a suction cup, eight biopsies were taken on four patients not included in the present study. The microscopic picture in general showed pools of extravasated blood between the bundles of collagen in the subpapillary layer (corium) of the skin. The red cells showed a tendency to grouping about small arterioles and sweat glands. Serial sections were not made, but one section showed an interruption in the wall of an arteriole, with blood extending from the lumen into the surrounding tissue. There was no associated inflammatory reaction. Similar biopsies done by Peck, Rosenthal, and Erf<sup>9</sup> showed dilated, moderately engorged capillaries in the papillary and subpapillary layers of the skin. Some of the vessel walls were ruptured. Spaces between endothelial cells in intact capillaries were widened. No inflammatory exudate was seen. There was fragmentation of elastic tissue in the area of hemorrhage.

#### DISCUSSION

Wolbach and Howe<sup>10</sup> explained the decreased capillary resistance and hemorrhages seen in experimental and clinical scurvy on the basis of a chemical alteration of intercellular substances. Johnson, Osborne, and Scupham<sup>11</sup> determined finger-volume changes during fever therapy by means of an air conduction plethysmograph. They obtained an increase in pulse-volume which was interpreted as increased circulation due to vasodilatation. Landis<sup>12</sup> concluded from his microinjection studies that "heat produces peripheral vasodilatation, raises capillary blood pressure conspicuously and, through relaxation of capillaries, increases the area of capillary wall available for filtration." Dilated capillaries are probably more easily ruptured than those of normal caliber. Also, with greater intracapillary pressure<sup>13</sup> it would seem that less extracapillary suction would be necessary to rupture the vessel walls. Hartman<sup>14</sup> showed that the pathologic changes resulting from fever therapy were typical of anoxia produced by prolonged asphyxia.

Wilson and Doan,<sup>15</sup> in a study of blood coagulating factors, concluded that the anoxia produced by artificially induced fever resulted in hepatic and megakaryocytic damage. This in turn caused a decrease in prothrombin alone or with fibrinogen, and a relative or absolute thrombocytopenia. In two of their patients epistaxis and hematemesis occurred at the point of greatest depression in circulating prothrombin and blood platelets. According to the theories on blood clotting, these factors are concerned not with hemorrhage, but rather with the clotting mechanism after hemorrhage occurs. Yet recent investigations have shown that the hemorrhagic tendency asso-

middle of the day, to take vacations frequently, to acquire a calm, philosophic outlook on life and to avoid nervous stresses and strains. Young individuals who follow occupations that are strenuous from a nervous standpoint may well consider it advisable to change to an occupation that is more restful.

Many diets have been advised for the treatment of hypertension, but there is very little evidence that diet influences blood pressure. We do not feel it advisable to restrict protein or salt in diets of hypertensive patients who do not have renal or myocardial failure. Individuals who are overweight should reduce, for obesity throws an additional strain on the heart by increasing the work that the heart must do, and as a result of deposition of fat in cardiac muscles and around the heart. Restriction of alcohol and coffee is not imperative unless they serve as stimulants. They do not in themselves increase the blood pressure appreciably. Smoking greatly increases the blood pressure of many patients who have hypertension, and if this can be demonstrated by having the patient smoke after his blood pressure has reached a basal value, it is well to consider sharp restriction or complete elimination of smoking.

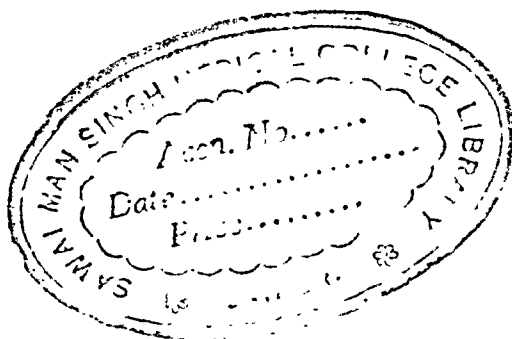
It is apparent that the methods of medical treatment available today are largely unsatisfactory, so far as reduction of blood pressure is concerned. That they have some value is apparent, but we believe that almost every physician who treats hypertension is dissatisfied with such therapeutic methods as are available to him today. Symptoms may be relieved rather easily, as Ayman<sup>26</sup> has pointed out. However, continued relief of symptoms may be considerably more difficult to accomplish than is temporary relief of them. This conclusion relative to failure of reduction of blood pressure by medical means is supported by the opinion of almost all those who treat patients who have high blood pressure under controlled conditions, by the high mortality caused by hypertension and by the number of physicians who consult other physicians or refer their patients to other physicians because the physician's own medical treatment has been inadequate. The situation regarding the medical treatment of hypertension is roughly comparable to that regarding pernicious anemia before the discovery of the efficacy of liver extract. It may surprise younger members of the profession to know that the present-day medical treatment of hypertension is much the same as that outlined 25 years ago by Elliott and that described 20 years ago by Moschcowitz.<sup>27, 28</sup> During the intervening period several million people have died of high blood pressure in the United States. The failure to change this type of medical treatment is patently not referable to the fact that this treatment has been satisfactory but to the fact that there has been nothing better brought forth.

Since the medical treatment of essential hypertension is largely unsatisfactory we have performed sympathectomies with the hope of relieving hypertension. This type of treatment has been employed on the bases of previous experiences with sympathectomies in the treatment of peripheral vascular diseases of vasospastic origin.

Sympathectomy is not carried out because we have assumed that the in-

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obtain some idea as to the values the blood pressure might attain as a result of nervous stresses and strains. In almost all instances we have determined the reduction of blood pressure resulting from the administration of drugs and also the reduction obtained by rest and sleep. Three grains (0.2 gm.) of sodium amytal has been administered hourly for three successive hours and a 5 per cent solution of pentothal sodium has been injected intravenously until such a time as the blood pressure has not decreased further.<sup>6, 7</sup> All the patients suffering from essential hypertension were classed into groups suggested by Keith, Wagener and Barker because such grouping gives us information about the severity of the hypertension, the effects of elevation of the blood pressure on the arteries, and about the prognosis. We wish to emphasize the fact that this grouping does not indicate the grade of hypertension present, although, usually, the hypertension of patients in each group (except the first, of course) was more severe than that of the preceding group.<sup>11</sup> The essential points of such classification are shown in table 1.

TABLE I  
Classification of Essential Hypertension

Group	Degree of Hypertension	Changes in Retinal Arteries	Retinitis	Edema of Optic Disks
1	Mild	Minimal	Absent	Absent
2	Moderate to severe	Moderate	Absent	Absent
3	Moderate to severe	Marked	Present	Absent
4	Severe	Marked	Present	Present

We have attempted to select patients for operation for whom the prospects of significant reduction in blood pressure would be greatest. Unfortunately, much interference with such selection was encountered because we have had to learn by experience which patients were most benefited and which were not, because many patients requested operation even though our studies indicated that they had little chance to benefit from such a procedure and because the best information which we had at the time did not always allow accurate prediction of results. We learned early in this study that it was useless to operate on patients who had congestive heart failure, auricular fibrillation, angina pectoris, significant renal insufficiency or severe hypertensive encephalopathy. In brief, it was evident that little could be accomplished when advanced arterial lesions were present. Albuminuria and slight to moderate enlargement of the heart were not considered contraindications to operation in themselves.

#### PREOPERATIVE PREDICTION OF EFFECTS OF OPERATION ON BLOOD PRESSURE

Since the blood pressure of some patients is not reduced by sympathectomy, whereas the blood pressure of other patients is greatly reduced by the operation, it is important, preoperatively, to attempt to select the patients

hypertension in general is not very serious. Such an attitude is wishful in part, for few physicians like to face the fact that there is no routinely effective treatment for hypertension. If the physician believes that hypertension is not a serious disease, failure to treat it satisfactorily will not be so disappointing. This belief in the benignity of hypertension neglects to take into account repeated observations such as those written in the preceding paragraph; namely, that hypertension usually is a serious disease which terminates the lives of those it afflicts within a relatively short span. Another cause for concern is the apparently decreasing age at which hypertension endangers the lives of those who are afflicted with it. This is a clinical impression based on the repeated observations that hypertensive members of a third generation die earlier than hypertensive members of the second generation of the same family, and that those of the second generation die earlier than those of the first generation; apparently all from hypertension. Not uncommonly on questioning, the physician finds a situation similar to the following: the grandfather died at 72 years of age of "stroke"; the mother died at 60 of "Bright's disease" and the son, aged 35 years, is seriously ill from hypertension which probably will terminate his life within a few months. All these observations emphasize the fact that hypertension is ordinarily a serious disease.

During the past few years there has been much progress in the production of hypertension experimentally and in understanding of the mechanism by means of which the blood pressure is elevated in such experiments. A prominent example is the notable achievement of Goldblatt,<sup>14</sup> who produced elevation of the blood pressure in animals by diminishing the blood supply to the kidneys. For these experiments, in which he produced a condition in animals closely resembling essential hypertension of man, Goldblatt received the Phillips Memorial Prize at the meeting of the American College of Physicians two years ago. It is unnecessary to refer specifically herein to others who have confirmed and extended Goldblatt's observations. The names of Page, Winternitz, Collins, Dock, Freeman, Houssay, Introzzi, Katz, Leiter, Nuzum, Prinzmetal, Rytand, Wilson, Landis, Pickering and Wood, are prominent in this field.\* We do not wish to detract from the excellent work that has been done on experimental hypertension and allied studies; rather, we wish to commend such work as being praiseworthy evidence that advances are occurring in a field of medicine in which little progress has been made until recently. We feel, moreover, that we will not detract from this excellent experimental work if we indicate that it has helped only slightly the clinician who must attend patients who have hypertension. We hope, also, that this statement will not be true for long. These few introductory remarks serve to emphasize the fact that hypertension is a common and serious disease, and that recent experimental studies have helped only insignificantly in the successful treatment of it up to the present time.

\* These contributions are reviewed in *Hipertensión Arterial Nefrógica; Estudio Experimental*. Ferrari Hnos. Buenos Aires, 1939.



TABLE II

Preoperative Prediction of Temporary or Poor Results Based on Studies in Vasodilation and on Observations of the Retinas

	Cases	Temporary or Poor Results, Per Cent
Minimal* diastolic blood pressure		
From rest		
<i>a.</i> More than 110	33	94
<i>b.</i> More than 120	13	100
From injection of pentothal sodium		
<i>a.</i> 105 or more	63	83
<i>b.</i> More than 115	18	90
<i>c.</i> More than 125	7	100
From administration of amytal		
<i>a.</i> 105 or more	31	94
<i>b.</i> 115 or more	10	100
Sclerosis of the retinal arteries, grade 3	17	100
Hypertension, group 4	7	100
Minimal systolic blood pressure resulting from rest		
<i>a.</i> 180 or more	29	93

\* The term "minimal" designates the lowest blood pressure resulting from various measures.

TABLE III

A Comparison of the Preoperative Reduction of Systolic Blood Pressure Resulting from Rest in Bed with Results Following Operation

Response of Systolic Blood Pressure to Rest, mm. of Mercury	Cases	Effects of Operation on Blood Pressure	
		Good and Fair, Per Cent	Temporary and Poor, Per Cent
Less than 140	63	48*	52
140-179	128	27	73
180-219	29	7	93

\* Indicates lowest blood pressure during rest.

TABLE IV

A Comparison of Preoperative Reduction of Diastolic Blood Pressure Resulting from Rest in Bed with Results Following Operation

Response of Diastolic Blood Pressure to Rest, mm. of Mercury*	Cases	Effects of Operation on Blood Pressure	
		Good and Fair, Per Cent	Temporary and Poor, Per Cent
100 and less	147	37	63
101-110	40	25	75
More than 110	20	6	94

\* Indicates lowest blood pressure during rest.

rather promptly. Of all the drugs commonly used in the treatment of hypertension, excepting potassium sulfocyanate, the sedatives are the best and of these phenobarbital is as good as any. The ideal sedative is one which will reduce nervousness and irritability but which will not interfere with the essential cerebral activities. Ordinarily,  $\frac{1}{2}$  to  $1\frac{1}{2}$  grain (0.032 to 0.1 gm.) of phenobarbital administered three times a day is advisable.

Potassium sulfocyanate has been used in the treatment of hypertension for several years.<sup>20, 21</sup> A relatively recent and important advance has been determination of the concentration of the cyanates in the blood.<sup>8, 22, 23</sup> The amount of this drug to be administered orally should be determined by frequent calculations of the concentration of cyanates in the blood. The concentration in the serum should range between 8 and 14 mg. in each 100 c.c. of blood. As little as a total of 5 grains (0.3 gm.) a week, or as much as 5 grains (0.3 gm.) three times daily, of potassium sulfocyanate, depending of course on the individual patient, must be administered to cause the aforementioned concentration in the blood. Such symptoms as headache, insomnia and nervousness may be relieved thereby. Blood pressure is reduced in about half the patients so treated.<sup>8, 22</sup> Fatigue, weakness, increasing nervousness, dermatitis, nausea, vomiting, anemia and enlargement of the thyroid gland may occur, even if administration of the drug is well controlled. Weakness and fatigue may occur early in the course of adequate treatment, but usually they disappear as medication is continued. After five to ten years of treatment, elderly patients who have severe grades of hypertension may have anemia, emaciation and muscular wasting, but it is not clear whether these conditions result from cyanate therapy or from hypertension itself. If the concentration of cyanates in the blood is too great, lethargy, mental confusion, psychosis, exfoliative dermatitis, weakness, difficulty of speech, convulsions and collapse may occur.<sup>8, 22, 24</sup>

Our experience with the use of sulfocyanate in the treatment of hypertension has been somewhat limited, but relief of symptoms such as headache is frequently striking. There is definite reduction of blood pressure in some cases. Potassium sulfocyanate never should be administered for a long period unless the amount administered is based on studies of concentration of cyanates in the blood of each individual patient. It is imperative that the physician prescribing sulfocyanates familiarize himself with the literature on the subject before treating the patient with the drug. Not only does the administration of potassium sulfocyanate help patients who have not undergone sympathectomy for hypertension, but in some of the cases in which little or no benefit has been obtained from this operation, the postoperative administration of potassium sulfocyanate has been followed by most gratifying results. Davis and Barker<sup>25</sup> have noted similar results.

Rest and the reduction of nervous stresses and strains are advisable in the treatment of many patients who have essential hypertension. In general, it is advisable for patients who have hypertension to obtain nine hours of rest in bed at night, to lie down for an hour or an hour and a half in the

medical supervision without benefit, provided clinical studies are satisfactory, whereas patients who have not had adequate medical supervision may be treated medically in order to evaluate the benefit to be derived from such a regime. However, they should not be treated medically for so long that they become unsatisfactory candidates for surgical treatment because of progression of the disease. Naturally, it is desirable to avoid performance of extensive sympathectomy on patients who are ill because of conditions, other than the hypertension, which may be incidental and relatively unimportant. For example, a patient affected by psychoneurosis or nervous exhaustion would not be cured of the condition even if her blood pressure were reduced by sympathectomy.

### RATIONALE OF SYMPATHECTOMY FOR ESSENTIAL HYPERTENSION

The sudden and permanent reduction of high blood pressures following the removal of benign pheochromocytomas from the adrenal gland as well as the frequent occurrence of hypertension among surgeons is responsible for the interest surgeons have taken in the problem of hypertension. The earlier surgical procedures consisted of denervation of the adrenal gland as well as subtotal section of the gland, the operations being based on the principle of attempting to reduce the amount of epinephrine secreted. Inasmuch as epinephrine produces vasoconstriction and inasmuch as extensive sympathectomy is capable of reducing vasoconstriction, surgeons began to speculate as to whether or not it would be possible to develop an operation that might denervate a vascular bed sufficiently large to alter blood pressures in a patient suffering from essential hypertension.<sup>36, 37, 38, 39, 40</sup> Since it has been proved that the peripheral arterial resistance has been reduced and that the flow of blood has been increased by performing extensive sympathectomy in Raynaud's disease, the operation, a bilateral ventral rhizotomy from the sixth thoracic to the second lumbar nerves, was proposed and performed at The Mayo Clinic in 1930. This operation was employed by a number of surgeons who obtained results justifying further investigation of the surgical approach to the problem of essential hypertension.

The operation of ventral rhizotomy<sup>41</sup> was performed on the basis of interrupting sympathetic nerve fibers which left the spinal cord by the way of the ventral roots to join the sympathetic ganglia and trunks before reaching the arterioles. Rhizotomy was extended from the sixth thoracic to the second lumbar nerves so that it would include all the fibers carrying vasomotor impulses through the lower half of the thoracolumbar sympathetic outflow in order to denervate the blood vessels or to interrupt vasoconstrictor impulses traveling from the central mechanism to the blood vessels supplying the lower half of the body. The operation was also devised to include the sympathetic innervation of the adrenal gland as well as the arterial supply of the kidney with the hope that any sudden dumping of epinephrine might be thereby prevented and that the circulation of the kidney would be in-

creased resistance to the flow of blood is localized to the splanchnic region. On the contrary, we accept the evidence that the increased resistance offered to the flow of blood through the arterioles is present over the entire body.<sup>29, 31</sup> If the surgeon is to accomplish the best results from the neurosurgical treatment of hypertension, he should sever the connections of the sympathetic nerves with almost all portions of the body. Unfortunately, this is impracticable or even impossible. We are aware, also, that clinical and experimental evidence is available to indicate that the sympathetic nervous system has little or nothing to do with the elevation of the blood pressure in essential hypertension.<sup>29, 30, 31</sup> Some of this evidence is acceptable and some of it is unacceptable. We may state parenthetically that clinical experimental evidence indicates that the sympathetic nervous system does not produce Raynaud's disease.<sup>32, 33, 34</sup> However, lumbar sympathectomy uniformly cures Raynaud's disease of the feet, and cervicothoracic sympathectomy cures Raynaud's disease of the hands, or at least, lessens it in a large percentage of cases. Moreover, extensive sympathectomy does reduce the blood pressure of many patients suffering from essential hypertension.<sup>7</sup> The fact that it does not do so routinely does not detract significantly from the observation that it does do so in some cases. Further, it is a common observation that, postoperatively patients experience sharp reduction in their blood pressures and marked acceleration of the rate of the heart when they stand.<sup>7</sup> Studies on the rate of flow of blood through arteries and veins of the extremities before and after extensive sympathectomy show that beyond doubt, this surgical procedure increases the rate of flow of blood.<sup>35</sup> These observations indicate that sympathectomy may modify the mechanism by means of which the blood pressure is elevated in essential hypertension.

#### METHOD OF STUDY OF PATIENTS WHO HAVE UNDERGONE EXTENSIVE SYMPATHECTOMY FOR ESSENTIAL HYPERTENSION

We have attempted to limit the neurosurgical treatment of hypertension to those patients who have essential hypertension. By careful study we have attempted to exclude patients suffering from primary nephritis, coarctation of the aorta, renal lesions such as atrophic pyelonephritis, Cushing's syndrome and benign pheochromocytoma of the suprarenal glands. The blood pressure of each patient has been determined hourly for 24 consecutive hours, for we are aware of the fallacy of using single determinations of blood pressure as a basis for judging results in such a study. The retina has been examined by an ophthalmologist who is particularly interested in the retinal findings in hypertension. Roentgenologic study of the size of the heart, electrocardiography and tests for renal function have been carried out almost routinely, but we are not reporting the results of these studies because they do not add significantly to the chief considerations, the effects of sympathectomy on blood pressure and on symptoms of hypertension, and because they were usually normal. The response of the blood pressure to immersion of a hand in ice water was determined in almost all instances to

valescing from sympathectomy, an acute gangrenous lesion of the gall-bladder developed which required an emergency operation, following which pneumonia developed. This patient succumbed, but was the only patient who died following an operative procedure.

In order more accurately to evaluate the results, we have not included thirty patients operated on within the past six months (at the time of writing), because patients almost universally have a pronounced reduction of blood pressure immediately following the operation. We were unable to secure replies to our recent inquiries of thirty-six patients. Ten other patients are not included in the study because splanchnic resection was included with other procedures such as unilateral nephrectomy, or because the operation was performed for patients suffering from hypertension and thromboangiitis obliterans or other accompanying diseases, in which cases it was carried out as an investigative procedure.

The study includes a review of postoperative results in 224 cases. Questionnaires were sent to patients and their physicians unless they had returned to the clinic for reexamination within three or four months prior to the time that the survey was made. The physicians were asked to fill out a questionnaire on blood pressure studies. The first reading was taken on the patient's entrance to the physician's office, a second reading was taken ten minutes later and a third reading was taken while the patient was standing. The first two readings were made while the patient was reclining and the third was made after the patient had stood in the erect position for one minute. The patients were requested to use the descriptive terms "yes" and "no" about each individual symptom before operation, and the descriptive terms "better," "much better," "slightly better," "unchanged" and "worse," relative to their symptoms at the time they received the questionnaire.

#### OPERATIVE EFFECTS ON BLOOD PRESSURE

Unless the patient is prepared for operation by the administration of a sedative, such as 3 grains (0.2 gm.) of pentobarbital sodium one hour prior to the administration of the anesthetic agent, the blood pressures will be found at their maximal readings. Occasionally they are so dangerously high that operation must be postponed. But once the patient has become thoroughly anesthetized the blood pressures recede to the preoperative readings made when the patient was at rest in bed. Resection of the splanchnic nerves and the lumbar sympathetic trunk immediately results in recession of blood pressure. The decrease is not so great after a unilateral operation as it is after the second operation which completes resection of the splanchnic nerves and the lumbar sympathetic trunks. Ephedrine is administered in doses of 0.025 gm. and physiologic sodium chloride solution is frequently given intravenously during the second operation in order to prevent surgical shock or complications arising from too excessive decreases in blood pressure. We attempt to maintain a systolic pressure of 100 mm. of mercury.

who will be benefited by operation and to refuse operation to those who cannot be benefited. Obviously, in order to influence blood pressure by sympathectomy, elevation of the blood pressure must have been caused by increased resistance of the arterioles, which can be reduced by sympathectomy. If, on the other hand, increased arteriolar resistance is the result of organic changes in the arterioles or of some pressor substance in the blood, sympathectomy would not modify the blood pressure unless it did so in some indirect way, such as by increasing the flow of blood through the kidneys, thus reducing the amount of pressor substance in the blood. To gain useful information, we divided our results, depending upon effect of operation on blood pressure, into three groups: (1) good, (2) fair and (3) temporary and poor. The last-mentioned group included all patients who had died, those who had hemiplegia, those whose blood pressures had returned to the preoperative value after having been reduced for variable periods, and those who had not benefited, even temporarily, from operation. Some patients have been operated on who would not be operated on now, but during much of our earlier experience we were more or less compelled to select patients by the method of trial and error.

As we have indicated previously, there are no methods of predicting results with certainty.<sup>5, 7</sup> However, there is a group of circumstances which indicate that the results of operation on blood pressure will almost certainly be temporary or poor.\* These circumstances, in brief, consist of inadequate reduction of blood pressure as a result of such measures as rest, advanced hypertension (group 4) and advanced arterial disease as exemplified by marked sclerosis of the retinal arteries (table 2). We believe that these patients should not be treated by sympathectomy for essential hypertension because the results of operation on blood pressure are almost uniformly disappointing. The more marked the narrowing and sclerosis of the retinal arteries are, the less likely are the results of operation on blood pressure to be good. Thus it is obvious that the results of operation in hypertension, groups 1 and 2, are better than in hypertension, group 3. The response of the systolic and diastolic blood pressures to rest influences results of operation (tables 3 and 4). The more nearly the systolic and diastolic blood pressures approach normal during rest and sleep, the more likely the results are to be good or fair. Unfortunately for accurate prediction, even when the systolic blood pressure has decreased to less than 140 mm. of mercury and the diastolic blood pressure has decreased to 100 mm. of mercury or less as a result of rest, some patients' blood pressures have been reduced only temporarily by operation. Similar results were noted in a study of the value, in predicting results of sympathectomy on blood pressure, of the administration of sodium amytal † and of the injection of pentothal sodium<sup>6</sup>

\* Since our studies indicate that the blood pressures of patients who have had results indicated as "fair" react essentially the same as do those who have had results indicated as "good," we have combined the two groups for simplification.

† 3 grains (0.2 gm.) hourly for three successive hours.

TABLE IX  
Effects of Sympathectomy on Blood Pressure (Good Results)

Blood Pressure					
Before Operation			Taken After Operation, Months	After Operation	
Maximal	Minimal	Mean		At Office Examination Only	After 10 Minutes' Rest
240/138	170/105	200/120	43	160/100	150/70
240/158	135/80	180/120	41	160/100	170/110
250/160	182/98	210/129	37	150/100	130/80
160/110	136/86	150/100	32	120/84	116/80
220/140	122/80	170/110	30	170/90	160/80
192/130	130/90	150/105	30	164/84	148/72
230/126	150/100	175/115	30	166/88	164/86
224/140	170/112	190/120	28	170/80	164/78
164/114	130/50	140/80	27	138/82	132/80
230/150	188/108		27	142/85	126/85
228/160	150/110	185/135	25	140/108	134/98
214/160	160/110	170/110	19	142/86	160/100
145/110	85/60	120/80	13	136/84	120/76
160/110	140/90	150/100	12	140/90	
190/130	136/96	150/115	10	135/85	
195/130	150/95	170/115	9	152/98	122/98
200/120	130/90	180/110	7	118/90	116/84
150/100	132/90		7	138/92	132/85
240/100	130/90	150/100	7	150/82	132/80
200/120	150/110	170/114	6	130/80	124/80
220/140	140/94	170/120	6	164/90	158/90
210/120	120/80	150/90	6	154/92	138/78
174/120	138/95	160/110	5	140/100	120/80
220/128	155/90	190/110	3	145/100	
200/144	135/100	170/110	3	130/86	120/84
210/155	176/110	190/135	3	150/108	
200/115		140/95	3	162/92	144/84

seems fair to compare "maximal" pressures determined at The Mayo Clinic with the pressures determined by the patients' physicians when they first came into the physicians' offices, for at the clinic the "maximal" pressures were almost always those determined at the time of the original examination. However, the "minimal" pressures determined at the clinic do not correspond to the pressures determined at the referring physician's office after ten minutes of rest on the part of the patient. The "minimal" pressures determined by us were the lowest pressures occurring during 24 hours of rest and sleep, and naturally they would be considerably lower than if the rest period had been only ten minutes. Some of the results which we have listed as "fair" might be considered "poor" by other observers, but some of them might also be considered good. The designation "temporary and poor" includes those patients whose blood pressures were as high at the time of our last study as they had been before operation. They are not designated "poor" alone because many of the patients included in this group had experienced marked reduction in blood pressures for many months after

TABLE V

A Comparison of the Preoperative Reduction of Diastolic Blood Pressure Resulting from Administration of Sodium Amytal with the Results Following Operation

Effect of Amytal on Diastolic Blood Pressure, mm. of Mercury	Cases	Effects of Operation on Blood Pressure	
		Good and Fair, Per Cent	Temporary and Poor, Per Cent
Less than 85	32	32	68
Less than 100	106	31	69
101-110	21	10	90
More than 110	11	0	100

on the diastolic blood pressure before operation (table 5). Analyses were made of various other data, such as mean and maximal systolic and diastolic blood pressures, but the results were essentially the same as those reported in the preceding tables (table 6). The conclusions to be drawn from this

TABLE VI

A Comparison of the Preoperative Maximal Diastolic Blood Pressure with the Results Following Operation

Maximal Diastolic Blood Pressure, mm. of Mercury	Cases	Results of Operation on Blood Pressure	
		Good and Fair, Per Cent	Temporary and Poor, Per Cent
Less than 115	26	58	42
115-134	84	33	67
135-154	83	20	80
155 or more	29	28	72

attempt to predict how well extensive sympathectomy will affect blood pressure in essential hypertension may be summarized as follows: The more nearly the blood pressure approaches normal as a result of rest, administration of sodium amytal and the injection of pentothal, and the less marked the vascular disease the more likely extensive sympathectomy is to reduce blood pressure significantly. However, even when responses of blood pressure are adequate and when vascular disease is minimal, extensive sympathectomy may reduce blood pressure only temporarily. When blood pressure is not reduced markedly by rest, administration of sodium amytal and the injection of pentothal sodium, when advanced vascular disease, renal insufficiency or congestive heart failure is present, it is useless to perform extensive sympathectomy for essential hypertension.

Additional factors may be considered when the decision is made as to the advisability of operation. Rapidly progressive hypertension seems to respond less favorably than slowly progressive hypertension does. Generally, patients with very high blood pressures (220 systolic and 130 diastolic or more, expressed in millimeters of mercury) respond unfavorably to sympathectomy. Operation is advisable for patients who have had adequate



tension, it is well to bear in mind the fact that hypertension is as deadly as cancer. The relief or amelioration of symptoms with the extension of the expectancy of life in the patients in advanced group may justify the surgical procedure, since many patients continue to experience clinical relief and are able to return to a gainful occupation even though blood pressure values have failed to remain normal.

### POSTOPERATIVE EFFECTS OF SYMPATHECTOMY ON THE CLINICAL SYMPTOMS

Although it is disappointing to see blood pressures return to preoperative values in patients, it is gratifying to see many of these patients remain free from clinical symptoms. The only explanation that we can give for the fact that patients had been free from symptoms even though preoperative pressure levels have returned is that the maximum pressures have not been reached, the so-called maximum ceiling of pressure has remained lower than before operation. It may also be due to a narrowing of systolic and diastolic range following operation. We are aware that internists have said that any active treatment is effective for a time in relieving symptoms and we grant that this might be true in early instances of the disease or instances in which the treatment includes forced rest in bed. Our experience has revealed that the patient who has a progressive disease will soon have a return of his symptoms. Therefore the increased relief of symptoms obtained by sympathectomy probably warrants performance of the operation occasionally in the patient whose condition is "borderline" and who does not respond to pre-

TABLE XI

Relief of Clinical Symptoms by Sympathectomy According to the Effects Produced on Blood

Postoperative Blood Pressure, Results	Headache			Dizziness			Tiredness			Thoracic Pain			Shortness Breath		
	Number of Cases			Number of Cases			Number of Cases			Number of Cases			Number of Cases		
	Better	Unchanged and Worse	New*	Better	Unchanged and Worse	New*	Better	Unchanged and Worse	New*	Better	Unchanged and Worse	New*	Better	Unchanged and Worse	New*
Good	15	1	0	12	0	2	10	7	1	6	1	1	10	4	5
Fair	28	1	0	17	3	1	13	10	1	7	4	3	12	8	5
Temporary or poor	67	18	4	56	5	4	53	36	8	20	14	12	37	32	12

\* This designation applies to symptoms noted only since operation.

operative vasodilating measures. Table 11 includes data from preoperative histories and replies to an examination or questionnaire. We again have tried to compare the clinical results with postoperative results in blood pressure. A review of table 11 shows in one line that although the reductions in

creased, thus preventing or minimizing the effects of an anemic kidney which results in the production of renin or angiotonin.

The laminectomy which is necessary to the performance of rhizotomy constituted a formidable procedure, one which was attended by considerable surgical shock. This prompted the development of other surgical technics, less formidable, with the hope of accomplishing the same results as rhizotomy. Inasmuch as subtotal section and denervation of the adrenal gland were of only temporary value in lowering blood pressure, the newer surgical procedures were devised to interrupt splanchnic nerves. The operation developed at The Mayo Clinic in 1935 consisted of resection of the splanchnic nerves with a portion of the celiac ganglion, resection of the upper lumbar sympathetic trunk, including the first and second lumbar ganglia, by a subdiaphragmatic extraperitoneal approach through separate incisions in the lumbar region not unlike those employed for operations on the kidney. Other accepted operations in use today consist of removal of the celiac ganglia as devised by Crile<sup>42</sup> and supradiaphragmatic resection of the splanchnic nerves on both sides as advocated and performed by Peet.<sup>43, 44</sup> Each procedure has its advantages and disadvantages. Since 1935 we have employed the subdiaphragmatic approach because it is attended by a minimum of surgical risk and because it permits the surgeon to include the sympathetic fibers which carry vasomotor impulses to the lumbar sympathetic ganglia. The inclusion of the sympathetic fibers of the lower end of the thoracolumbar outflow which travel over the two upper white lumbar rami is significant, we believe, since it interrupts the central impulses to the adrenal glands and renal arteries. The operation, unfortunately, does not include those midthoracic fibers that may travel along the aorta and it is very possible that Smithwick's suggestion of combining subdiaphragmatic removal with transdiaphragmatic removal of the splanchnic nerves, with the upper two lumbar ganglia on each side, may prove to be the operative procedure of choice, since it also includes the sympathetic filaments that follow the aorta.

#### RESULTS OF THE POSTOPERATIVE STUDY

To evaluate the results of (1) subdiaphragmatic resection of the splanchnic nerves, with resection of the celiac ganglion where these fibers enter the ganglion, with (2) resection of the lumbar sympathetic trunk, including the first and second lumbar ganglia on both sides, in the treatment of essential hypertension, we have made every effort possible to have the patients return for reexamination or to have them submit to reexamination by their local physician and to have him report on observations of blood pressure as well as to have the patient report on his own observations. This has been done to as late a date as January 1, 1940, a study extending over a period of five years. This includes a series of 300 patients who have submitted to 600 independent operations with no deaths. In one patient, who was con-

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The pressures will remain below normal for a week, at the end of which period they gradually increase to preoperative values obtaining when the patient was at rest in bed when sodium amytal was administered. All patients experience a marked decrease in blood pressure when they first become ambulatory following their operation. This is accompanied by tachycardia for several months, a phenomenon which we believe is caused by a diminished flow of blood into the heart resulting from the forces of gravity responsible for the accumulation of blood in the denervated vessels which have dilated and acted as reservoirs. This phenomenon is more pronounced in the patient who is free from arterial sclerosis than in the one with definite evidence of beginning sclerosis. Approximately two months following the operation the tachycardia and the excessively low pressures adjust themselves so as not to interfere with the patient's routine.

#### POSTOPERATIVE EFFECTS OF SYMPATHECTOMY ON BLOOD PRESSURE

The results are summarized in tables 7 and 8. There may be some question as to the classification of the results as "good" or "fair" in some of

TABLE VII  
The Effect of Sympathectomy in Reducing Blood Pressure  
in the Group of 224 Patients

Postoperative Blood Pressure, Results	Number of Cases	Percentage
Good	27	13
Fair	41	18
Temporary	87	39
Poor*	69	30
Total	224	100

\* Includes 34 patients who have died during the five years and 6 who have hemiplegia.

TABLE VIII  
A Comparison of Postoperative Effects on Blood Pressure (in Percentages) Obtained in the  
Respective Groups of Hypertension in the Group of 224 Patients

Group of Hypertension	Effect of Operation on Blood Pressure*	
	Good and Fair	Temporary and Poor
1 (11 cases)	45	55
2 (137 cases)	33	67
3 (69 cases)	26	74
4 (7 cases)	0	100

\* All figures represent percentages.

the instances. We realize that such classification is a matter of opinion. That the reader may judge for himself, we are reporting individual results in the groups indicated as "good" and as "fair" (tables 9 and 10). It

# THE ACTIVITIES OF THE AMERICAN COLLEGE OF PHYSICIANS IN GRADUATE MEDICAL EDUCATION \*

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DURING recent years interest in graduate medical education has increased steadily. Practitioners in the clinical branches recognize the fact that medical knowledge changes and that methods of practice should change also and with as little lag in application as possible. Thus the demand from practitioners for opportunity and guidance, in what Bruce has aptly called continuation study. Moreover, current graduates in Medicine no longer consider their education completed when the medical degree is conferred. Medical education and training for medical practice, whether the latter be general or confined to a special field, are recognized as continuing processes. Reflections of this point of view are to be found in the activities of some of the medical schools, but more conspicuously perhaps in the activities of organizations composed of practicing physicians and surgeons. Let us examine briefly some of the factors responsible for the current interest in extending the medical graduates' instruction beyond the formal courses prescribed by the medical schools.

Certainly one factor in producing the increased demand for graduate medical training resides in the superior quality of the recent graduates of medical schools. The care exercised by the schools in selecting students for admission results, undoubtedly, in improving the quality of the graduates. These graduates are mature men and women who have completed successfully a carefully planned and executed educational program in a highly competitive field. It is not surprising that individuals of this type recognize the importance of supplementing the basic knowledge acquired in the medical school by practical, vocational training in hospitals to the end of developing competency in practice. Hence, the medical school graduate now invariably includes hospital training in his program of organized medical instruction. Moreover, medical school faculties no longer consider that the instruction afforded students by the medical school is sufficient in itself to qualify graduates for practice. Some faculties have developed the philosophy that the university medical school is concerned primarily with providing a basic medical education, which the student may utilize in medical practice, medical research or simply as an educational discipline. Many medical educators state that they no longer attempt to provide medical students with vocational training. This responsibility, it is pointed out, is assumed by other agencies. The medical schools of the future, one dean states, will place even more emphasis upon basic medical education and less upon vocational train-

\* Read at the Cleveland meeting of the American College of Physicians April 1, 1940.

operation. Even temporary reduction of blood pressure of several months should increase expectancy of life and delay disastrous arterial changes.

The effect of sympathectomy on the permanent reduction of blood pressures is somewhat disappointing. However, the effect is approximately that

TABLE X  
Effects of Sympathectomy on Blood Pressure (Fair Results)

Blood Pressure					
Before Operation			Taken After Operation, Months	After Operation	
Maximal	Minimal	Mean		At Office Examination Only	After 10 Minutes' Rest
210/124	140/100	170/110	55	180/110	170/110
235/125	130/85	180/105	50	200/110	190/110
200/130	145/90	170/100	49	188/105	175/100
204/140	145/100	170/110	48	155/110	155/110
220/150	170/120	190/130	47	160/116	154/112
220/120	140/100	180/110	46	178/105	172/105
228/142	170/108	190/120	40	190/108	220/120
168/92	132/90	150/100	36	158/100	
200/135	148/110	140/94	35	146/108	130/98
234/142	142/102	165/113	35	184/106	176/112
180/110	140/95	145/100	30	176/100	152/108
170/118	110/70	135/90	30	160/108	154/106
220/140	156/92	188/136	30	170/110	160/108
198/126	144/90	160/100	29	195/100	180/100
235/140	156/100	195/120	29	155/108	158/110
220/114	170/98	190/110	27	174/96	172/92
184/118	120/85	130/90	27	160/100	152/98
220/110	170/100	190/110	26	185/105	180/100
290/120	120/75	150/100	26	152/104	143/104
185/110	110/70	140/95	25	170/98	170/98
220/90	164/86		24	160/110	160/105
210/140	110/95		24	190/110	162/100
170/120	120/70		24	180/96	136/90
210/140	150/100	170/120	23	142/120	150/100
170/120	125/80	145/95	23	180/96	
218/140	160/100	170/110	19	190/100	160/100
190/120	136/100	160/110	17	158/100	140/100
210/168	130/80	168/128	17	150/110	150/100
220/120	140/94	160/110	15	168/108	170/110
160/110	132/80	145/90	14	150/100	
220/160	138/96	150/110	12	156/108	
185/115	135/85	155/100	9	160/104	140/100
200/120	145/90	173/110	8	156/100	148/96
190/100	135/90		7	146/102	118/94
220/160	160/105	180/120	5	170/110	150/110
190/110	140/90	150/100	5	170/100	170/100
230/130	140/80		4	186/108	
200/130	150/100	175/115	4	180/110	168/106
195/120	120/65	160/105	3	160/100	
204/140	130/90	160/110	3	180/116	174/116
190/120	160/94	170/100	3	200/96	164/96

which earlier experience taught us to expect. The results which we have reported might be considered excellent if they concerned, for instance, the surgical treatment of cancer. When they are considered in relation to hyper-

The influence of this Council is an expression of the influence of the membership of the American Medical Association. It operates under no other authorization; its enforcement or disciplinary power resides solely in the strength of the medical opinion it represents. Current medical opinion regarding the desirability of graduate training and continuation study for physicians is unmistakably affirmative.

As specialization in medical practice evolved, special societies came into existence. The American College of Physicians is composed of some 4000 individuals especially interested in Internal Medicine and the medical specialties. One of the stated objectives of this College is to maintain and advance the highest possible standards in medical education, medical practice and medical research . . . to maintain the dignity and efficiency of Internal Medicine in its relation to public welfare. The efforts of our organization to attain these objectives are represented by (1) the annual meetings—post-graduate assemblies; (2) the provision of research fellowships; (3) the publication of the *Annals of Internal Medicine*; and (4) the sponsorship of continuing professional education in the form of graduate courses in Medicine.

Membership in the College is contingent upon certain requirements over and above graduation from an approved medical school. Among others there is a requirement regarding graduate training. The graduate of the medical school who aspires to membership in the College must avail himself of graduate training. The American College of Physicians and the section on Medicine of the American Medical Association sponsored the creation of the American Board of Internal Medicine. This Board, made up of representatives from the Section on Medicine of the American Medical Association and the American College of Physicians, certifies as to the competency of candidates appearing before it to practice Internal Medicine as a specialty. This Board requires that, to be eligible for certification, candidates must have adequate training.

Thus, the American College of Physicians, through its requirements for admission, and the American Board of Internal Medicine, through its eligibility requirements, stimulate graduates of medical schools who plan careers in Internal Medicine to seek graduate training. The Board of Regents of the College has recognized the obligation it assumed in thus creating additional demands for graduate training in Internal Medicine. To the end of meeting this obligation, in part at least, it set about in 1938 to determine how it could improve the training obtained by the hospital intern, assistant resident and resident in Medicine. The American Board of Internal Medicine feels also that, in this field of graduate training, it has interests and obligations. In approaching the problem the College and the American Board were impressed immediately by the importance of the work which the Council on Medical Education and Hospitals of the American Medical Association initiated in 1936, when it began its survey of hospitals to determine their fitness for special training in the specialties. Moreover, our Regents were cognizant of the contribution which the College of Surgeons makes in its

blood pressure have been temporary or poor the clinical relief has continued. Table 12 represents a summary of clinical relief obtained.

TABLE XII

Relief of Clinical Symptoms by Sympathectomy: Percentages Are Obtained by Comparing Preoperative and Postoperative Data

Postoperative Blood Pressure, Results	Headache	Dizziness	Tiredness	Thoracic Pain	Shortness Breath
	Percentage of Cases in Which Relief Was Obtained				
Good and fair	94	90	58	72	65
Temporary and poor*	79	92	60	59	54

\* Relief of symptoms at time when blood pressure had returned to preoperative value.

### SEQUELAE

Our recent studies of the sequelae following sympathectomy for essential hypertension are not unlike those previously reported, and therefore we will not review them at this time.<sup>45</sup>

### CONCLUSIONS

1. The results of operation for essential hypertension can be predicted with reasonable certainty by observing the response of the blood pressure to rest and sleep, to the ingestion of sodium amytal and to the intravenous injection of pentothal sodium. When poor results of operation are predicted as a result of these tests, the results are almost uniformly unfavorable. When good results are predicted, some patients do not receive as much benefit from operation as was anticipated.
2. There have been no operative deaths in a series of 300 cases. The operation itself does not disable, although anhidrosis of the lower extremities and loss of ejaculation and probably of fertility of the male patient result. Female patients have borne children following the operation.
3. Clinical symptoms invariably disappear with reduction of blood pressure, but in a number of instances the patient continues to be free from symptoms even though there has been a gradual return of elevated blood pressures.
4. Our experiences justify continuance of the operation in the treatment of essential hypertension. The individuals who will receive the most benefit from surgical treatment are those who seek treatment early in the course of their progressive disease, before irreparable damage has resulted to the cardiorenal vascular tissues.

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(b) To consider those elements which are regarded as essential in the appraisal of residencies, fellowships and systematic graduate courses for which the approval of the constituent organizations may be sought.

4. Actual visitation of medical schools and hospitals for the purpose of securing information regarding standards and facilities for instruction in Internal Medicine shall in general be made by the staff of the Council on Medical Education and Hospitals; the Council will, however, welcome the assistance of qualified representatives of the College and the Board when such assistance is available. Information thus obtained shall be made regularly available to the Conference Committee.

5. Residencies, fellowships or systematic courses in the field of Internal Medicine will be considered by the Conference Committee before independent action is taken by any one of the constituent organizations.

While the foregoing memorandum covers the situation as far as the Committee understands the matter delegated to it, it is the feeling of the Committee that it may well be desirable to include members of other medical specialty boards in a conference pertaining to the problems of graduate training.

The Conference Committee, which is proposed in this memorandum, has been created. It should make it possible for the College and the American Board of Internal Medicine to participate in the definition of the standards by which Council field workers evaluate medical internships, residencies, fellowships, etc. Moreover, the Conference Committee will have the opportunity to review the results of the field work and to make recommendations to the Council on Medical Education and Hospitals relative to its approval or disapproval of medical internships, residencies, fellowships, etc.

The Conference Committee has held its organization meeting and there is good reason to believe that through it the College will be influential in determining the quality and number of internships, residencies, and fellowships available for graduate training in Medicine. This contribution by the College to graduate education in Internal Medicine will be related in a natural, logical way to the traditional functions of the Council on Medical Education and Hospitals of the American Medical Association and to the interests of the American Board of Internal Medicine. If the objectives of the Conference Committee on Internal Medicine are attained, this method of co-operative work with the Council on Medical Education and Hospitals of the American Medical Association may be employed by other special societies and certification boards.

The Regents and Governors of the American College of Physicians and the Committee on Postgraduate Education have considered other means by which the College may create or improve facilities for special training in Medicine. Topics which have been considered in this connection are: (1)

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# CASE REPORTS

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## THE CLINICAL ASPECTS OF CARDIAC INVOLVEMENT (RIGHT AURICULAR TUMOR) IN IDIOPATHIC HEMORRHAGIC SARCOMA (KAPOSI'S DISEASE) \*

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PRIMARY involvement of the heart in Kaposi's disease never has been reported as such, insofar as can be determined. That cases of this type have occurred, however, is evident from the study of the original tissue. This type of involvement is suggested when the histological description of a cardiac neoplasm is characterized by sarcomatous tissue infiltrated with much hemorrhage. The two cases of this type which form the basis of this report were diagnosed as Kaposi's disease at autopsy.

Both cases have presented similar, and at the same time unusual clinical pictures. The first case presented all, and the second case presented many of the characteristics necessary for antemortem diagnosis. Although these tumors admittedly are rare, their clinical diagnosis is of interest.

In the two cases here reported, the clinical syndrome, supported by post-mortem findings which were almost identical in the two cases, seems definite enough to warrant its establishment as a distinct entity. The present paper analyzes the features of the cases reported here and of similar cases in the literature.

### LITERATURE

Cases of the type discussed in this paper are reported in adequate enough numbers in the literature to present an interesting background for the present cases. Raw,<sup>1</sup> in 1898, reports the case of a 43 year old charwoman who experienced pain in the chest, dyspnea upon exertion and who "had to sit up in bed at night three and one-half years before admission" even though she was able to do a little work until two months before admission. Admitted to hospital because of marked pain in the right chest, upon examination she was found to have an anxious expression, orthopnea, and marked dyspnea of a spasmodic character. Ascites, edema of the legs, enlargement of superficial veins of the thorax, dullness of the right chest and enlargement of the liver also were present. At autopsy a tear was found in the inferior vena cava just before its entrance into the right auricle, and a large, hard sarcomatous tumor, three by three inches, was present in the right auricle. This growth extended directly down the course of the inferior vena cava and terminated on the under surface of the liver as distinct hard nodular masses.

Norton's patient,<sup>2</sup> a 29 year old white male, was taken ill two days before admission to the hospital, with cough and bloody sputum which became rusty on

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ing. "The basic medical course is the doorway through which men pass to all the fields of Medicine. It constitutes the most powerful influence tending to unite the varied fields of medical work."\* The emphasis here is certainly not upon vocational or professional training. The university, according to this concept, has no obligation to the public regarding the technical fitness of its graduates for practice. Thus the graduates look elsewhere for vocational or practical training. Those graduates who aspire to practice are deeply concerned with this. They demand graduate or vocational training in the form of hospital staff positions.

Medical graduates are influenced by other agencies than their schools to acquire graduate training. Among these are the state and national boards of medical examiners. These boards, by their requirements for licensure or approval, emphasize the importance of graduate training. The national board and many of the state boards will not accept as candidates for examination medical graduates who have not had at least one year of graduate training as hospital interns. This requirement doubtless acts as an incentive to many students to acquire even more extensive training. If "at least one year" is required, does this not indicate the boards' opinion that two or three or more are desirable? Certainly more extensive training is desirable if the students aspire to any type of specialized practice. The requirements of the American certification boards dispel all doubt regarding this point.

The attitude of the general public also creates demand for graduate training for practitioners. All types of health service, public and private, are undergoing close scrutiny by the layman. Medical news is no longer found exclusively in professional journals. The public is deeply interested in medical news, scientific or otherwise. The daily and weekly newsorgans attempt to satisfy the demand. Moreover, the layman knows where his young doctor graduated in Medicine and where he served his internship and whether he continues to keep abreast by attendance on medical meetings, postgraduate assemblies, formal courses for continuation study, etc. The doctor is not a person set apart in the community and accepted uncritically because M.D. appears after his name.

More important than any other factor in creating the demand for adequate graduate training is the desire of the profession to elevate the standards of medical practice. The contribution of the American Medical Association in the field of medical education, through its Council on Medical Education and Hospitals, should be a source of pride to every member. Its most outstanding work has been in undergraduate medical education. The American Medical Association has played a conspicuous rôle in the evolution of medical education in this country. I believe that the medical schools of the United States are superior to those of any country in the world. The educational requirements for admission to these schools, the content of the curricula, the facilities for laboratory and clinical study have been made the subject of review and evaluation by the Council on Medical Education and Hospitals.

\* Dr. C. Sidney Burwell, Dean, Harvard Medical School.

During the next several weeks the patient continued to cough frequently, the cough being very distressing and appearing chiefly at night. Night sweats were frequent and marked.

On December 27, 1927, the patient was admitted to the George Washington University Hospital. Here his temperature was found to range from 101° F., to 102° F., maximum. He was constantly orthopneic. Twenty-four hours after admission there was epistaxis followed 24 hours later by slight hemoptysis.

A roentgen-ray examination of the chest revealed marked enlargement of the pericardial sac both to right and left. Within the right half of the cardiac shadow was a vertical shadow in the region of the right auricle, the nature of which, however, was not obvious. A six-foot film with the patient in the prone position showed marked widening of the cardiac shadow at the base.

Upon aspiration of the pericardium December 29, 1937, 3 c.c. of a bloody serous fluid were removed. After centrifuging, the erythrocytes formed a shallow layer in the bottom of the test tube. The supernatant fluid was clear and xanthochromic. No bacteria were visible in gram-stained sections. In a Wright-stained film erythrocytes predominated. The few leukocytes present were approximately 75 per cent lymphocytes and 25 per cent polymorphonuclear cells.

Fifteen hours following the first pericardial tap, the patient meanwhile having continued orthopneic and uncomfortable, a second pericardial tap was done. On this latter occasion, three hours before death, 700 c.c. of a bloody serous fluid were removed. Prior to tapping the patient's blood pressure was 120 systolic and 110 diastolic and he complained of severe pressure upon the anterior chest. Following removal of the pericardial fluid the blood pressure was practically unobtainable, only an occasional sound being audible between 80 and 70 millimeters of pressure. During the early period of the paracentesis the patient's respiration improved considerably, but as the aspiration continued he passed slowly into a condition of shock, becoming unconscious, and perspiring profusely. He became gradually more dyspneic, orthopneic, and very cyanotic, with no pulse obtainable at the wrist. He died suddenly two hours after the paracentesis.

Autopsy done four hours after death showed the following: The body was that of a well nourished male. Lips and gums were cyanotic. The neck was full. The vessels of the neck stood out prominently. About 1000 c.c. of amber colored fluid were present upon opening the abdominal cavity. The abdominal organs showed evidences of chronic passive congestion. The spleen was slightly enlarged, weighing 190 grams. Both kidneys were of normal size and appeared congested. The liver weighed 1850 grams and upon cut surface showed marked mottling from yellow to purplish red. The gall-bladder contained no stones and bile escaped freely through the bile ducts.

The left pleural cavity contained about 800 c.c. of blood-tinged fluid. The left lung was almost completely collapsed, presenting numerous areas of atelectasis and a few small infarcts in the lower lobes, mostly near the periphery. The remaining lung tissue showed chronic passive congestion. Practically all of the branches of the pulmonary artery were occluded by thrombi.

The right pleural cavity contained about 1000 c.c. of blood-tinged fluid and the right lung presented changes identical with those in the left lung.

The pericardial cavity was markedly dilated and contained approximately 900 c.c. of bloody fluid. The heart (figure 1) was enlarged, especially the right auricle, which occupied almost the entire anterior surface and measured 10 by 12 cm. in diameter. The heart weighed 725 grams. The pericardial surface of the right auricle was hemorrhagic and markedly roughened. The right auricle was almost completely occluded by a large mass firmly attached to the wall. The tumor was very hard and cut with marked resistance. The peripheral portion of the tumor, upon section, was

annual survey of the facilities for hospital training for Surgery and the surgical specialties and considered that the College of Surgeons by its very nature was preëminently qualified to determine standards for surgical internships and residencies and to evaluate hospital positions on the basis of these standards. Thus, it appeared to the Regents that the American College of Physicians could assay to render its contribution to the problem of graduate training for internists either in coöperation with one of the two organizations already in the field or as an independent enterprise. Invitations were extended us by both the American College of Surgeons and the Council on Medical Education and Hospitals of the American Medical Association to relate our interests to theirs. After much deliberation the Regents concluded that it would be unwise for the College to make its contribution either independently or as a coöperative enterprise with the American College of Surgeons, since in either instance it would duplicate work already started by the Council on Medical Education and Hospitals of the American Medical Association. Moreover, it was apparent that the interests of the American Board of Internal Medicine also were concerned in the matter. Therefore, an effort was made, at the invitation of the Council on Medical Education and Hospitals of the American Medical Association, to evolve a plan by which the Council, the College and the American Board could coördinate interests in a mutual undertaking. Tentative proposals, regarding the organization of a Conference Committee, were submitted by representatives of the three bodies concerned. It is hoped that by means of this Committee, the American College of Physicians and the American Board of Internal Medicine can participate in the work of the Council in surveying residencies, assistant residencies, internships and fellowships in Medicine, utilizing the existing machinery of the Council. The memorandum on the organization of of this *Conference Committee* of the Council on Medical Education and Hospitals of the American Medical Association follows. It has been approved by the Board of Regents of the College, the American Board of Internal Medicine, and the Council on Medical Education and Hospitals of the American Medical Association.

THE PROPOSAL FOR ESTABLISHING A CONFERENCE COMMITTEE CONCERNED  
WITH GRADUATE TRAINING IN THE FIELD OF INTERNAL MEDICINE

1. It is proposed that there be created a Conference Committee on Graduate Training in Medicine.

2. The Conference Committee shall consist of two delegates from each of the following organizations: The American College of Physicians, the American Board of Internal Medicine, and the Council on Medical Education and Hospitals of the American Medical Association.

3. The function of the Conference Committee on Graduate Training in Medicine shall be:

- (a) To submit observations and recommendations which may be useful in furthering the purposes of the constituent organizations.

Hyde and Ross Morris. Four months before admission the patient had noticed a slightly increasing general weakness to which he paid little attention. Two months before admission he developed what was believed to be a typical case of influenza characterized by malaise, generalized weakness and cough. After five days of rest in bed he attempted to return to work, but was unable to continue working because of weakness. Examination at that time showed an increased heart rate, and roentgen-ray examination of the chest showed cardiac enlargement. Following bed rest again, he lost ground rapidly and died on November 14, 1937.

Physical examination at the time of admission to the hospital revealed generalized glandular enlargement, cardiac enlargement and no murmurs. The liver was enlarged three fingers'-breadth below the costal margin. This enlargement increased to five or six fingers'-breadth at the time of death. Temperature ranged during his stay in the hospital from 96° F., to a maximum of 101° F. Pulse rate varied from 100 to 110 and respiratory rate remained around 22. Blood pressure was 115 systolic and 80 diastolic. Erythrocyte count on admission was 3.9 millions, hemoglobin was 70 per cent and leukocyte count was 5,100. At autopsy the body was that of a well developed and well nourished white male. Upon opening the peritoneal cavity the liver was found to extend from five to six fingers'-breadth below the costal margin. Two thousand c.c. of bile-tinged fluid were present. Numerous small hemorrhagic spots were noted throughout the omentum. These nodules ranged in color from light to dark brown and give a granular sensation upon palpation. The abdominal organs showed evidences of chronic passive congestion. The spleen weighed 95 grams and upon section whitish nodules on the surface were seen to extend several millimeters into the parenchyma. The right kidney contained a hemorrhagic nodule 1 cm. in diameter. On section the mass appeared to be a fairly recent infarct. Petechial spots were scattered irregularly over the surface of the kidney. The left kidney likewise showed petechial spots and several infarcts. The liver weighed 2070 grams and its capsule was thickened somewhat. In the center of the right lobe near its lower quadrant there was a nodular area about 1 cm. in diameter, which was redder in color than the surrounding liver parenchyma, but which was separated from it by a white zone. Several similar nodules ranging in diameter from 0.5 to 2 cm. were found throughout the liver. The gall-bladder was normal. The right pleural cavity contained 2000 c.c. of bloody fluid. Numerous areas, hemorrhagic in appearance were noted throughout the right pleural cavity. Similar areas of hemorrhagic extravasation were seen on the pleural surface of the right lung, which also showed on cut section infarcts and areas of atelectasis. The right lung was densely adherent to the mediastinal structures and pericardium by hemorrhagic nodular masses which were scattered rather diffusely in this area. The left pleural cavity contained 100 c.c. of clear straw-colored fluid. Changes in the left lung were similar to, but less obvious than those in the right lung.

The pericardium was firmly adherent to the heart which latter showed marked enlargement. The pericardium was markedly thickened, but could be removed with difficulty, revealing a red hemorrhagic surface with an enormous amount of fibrous connective tissue. The mediastinal lymph nodes were adherent to this fibrous hemorrhagic mass. On transverse section the myocardium was hemorrhagic and mottled and was involved by the hemorrhagic neoplastic tissue. A large nodule of the neoplastic tissue extended into the left auricle. The right auricle was almost completely obliterated by a hemorrhagic neoplastic mass. At the apex of the right ventricle was a smaller mass of neoplastic tissue. The left auricle showed no abnormalities. The left ventricular wall was markedly thickened. In the region of the apex the hemorrhagic neoplastic tissue invaded the myocardium of the left ventricle (figure 2).

the sponsorship of regional meetings of the College featuring educational programs in those sections of the country where this seems indicated; (2) the production of talking picture clinics and demonstrations for use at the regional meetings; (3) the establishment of American College of Physicians Fellowships at carefully selected medical schools and hospitals to the end of increasing the number of desirable positions available to recent graduates for graduate training in Internal Medicine and the basic medical sciences. A thoughtful consideration of this program by the Fellows is coveted by the Board of Regents, the Governors, and the Committee on Postgraduate Education. Certainly the College can make no more important contribution to the American public and the medical profession than by providing ways and means for men to increase their knowledge of and competency in Internal Medicine.



Upon microscopic examination the hemorrhagic neoplastic tissue presented a similar appearance regardless of the site from which it was obtained. The tissue was made up of spindle-shaped cells, varying in size, among which were many small blood vessels and a considerable amount of hemorrhage (figure 3). Occasional portions of the tumor showed areas of necrosis and occasionally mitotic figures were seen.

### DISCUSSION

Clinical characteristics presented by both of the cases here reported were rather those of chronic or subacute respiratory infection than otherwise. Norton has emphasized this aspect of cardiac tumors in his report. In the first case here reported, during the period of several months prior to hospitalization the patient developed increasing weakness, marked cough particularly during the night, varying amounts of sputum which was occasionally blood-tinged, and profuse night sweats. As termination of the disease approached, the mild jaundice present some two months previously decreased in intensity but never entirely disappeared. The nocturnal dyspnea and orthopnea increased in severity, and upon several occasions the nocturnal cough was productive of blood. The second of these two cases was practically identical except that in the terminal stages the evidences of respiratory infection were the outstanding symptoms.

A characteristic physical sign in both of the present cases was the peculiar edematous appearance of the face and neck. Although the skin seemed of normal texture it had taken on a wax-like appearance and seemed stretched over an increased amount of subcutaneous tissue. The facial edema was not so characteristic in the early stages, but by the time the patient was admitted to the hospital its characteristics were unusual enough to call forth comments from all observers and to be a factor in considering similar types of involvement in the two cases. Cyanosis never was particularly marked, but remained definitely noticeable throughout the course of the illnesses. The physical signs upon examination of the heart revealed little abnormality. Rate and rhythm remained normal in both cases and the sounds showed little variation from normal.

In comparison with the above clinical course the syndrome associated with myxomata of the left auricle as discussed by Bordley seems only suggestively distinctive. The palpitation, dyspnea upon exertion, and weakness, recurring in the episodes with intervals of freedom, as in Bordley's cases, are symptoms common to many types of disturbance. In addition these are symptoms which occur towards the end of the clinical course.

As mentioned by Yater<sup>8</sup> the accumulation of bloody fluid in the pericardial sac is highly presumptive evidence of a tumor of the heart. We should like to qualify and amplify this statement as follows. In the presence of bloody pericardial fluid, separation of cellular and liquid fractions should be done immediately upon obtaining the fluid. A relatively small proportion of intact erythrocytes in comparison with xantho-chromic supernatant fluid thus is of marked diagnostic value in these cases. Little attention seems to have been paid to this most important characteristic of pericardial fluid in this type of case.

In the case where the tumor involves the right auricle obviously it is difficult, upon roentgen-ray examination, for the individual unfamiliar with cardiac appearances to diagnose the nature of the right auricular tumor. In the Cabot case the increase in size of the tumor in the right auricle was traced in repeated roentgen-ray examinations. Six months before the patient was admitted to

the next day. There was moderate cyanosis, but examination of the heart revealed no especial abnormalities. While hospitalized the patient improved during the first week, but later became confused, morose and then delirious. The tumor in this instance was a large one filling the entire left auricle and extending down into the mitral orifice. The histological characteristics, from the description, were those of Kaposi's sarcoma.

A third patient, reported as a Cabot Case and discussed by Drs. Breed, Sanderson, Mallory and Holmes<sup>3</sup> was a 33 year old white female. During the two years preceding admission to hospital the patient had suffered attacks of substernal oppression and breathlessness. Seven months before admission cough, fever, and chest pains appeared. No hemoptysis was noted, but the dyspnea increased to such an extent that the patient was bedfast most of the time. Roentgen-ray examinations prior to one week before admission were negative, while the one taken at that time showed a lobulated mass in the region of the right auricle. Histological examination of the tumor, both as is reported in the literature, and as is agreed upon following interchange of sections with Dr. Mallory, shows the tumor to be a Kaposi sarcoma.

Clerc and Colleagues' patient,<sup>4</sup> a 34 year old white female, likewise presented the symptoms noted above. Binder<sup>5</sup> reports a case of tumor of the right auricle in which edema, beginning originally in the face and then spreading downwards, was a prominent feature. Ehrenberg<sup>6</sup> reports similar clinical findings in his case.

Bordley<sup>7</sup> reports the following clinical syndrome associated with myxoma of the left auricle. Onset is characterized by palpitation, dyspnea upon exertion, and weakness. These episodes at first occur about one week apart, and after awhile are a constant accompaniment of exertion. Later orthopnea and paroxysms of cough, together with other signs of left heart failure, appear. There is no response to rest or digitalis.

#### CASE REPORTS

*Case 1.* V. M., a 30 year old white male, was seen first on November 28, 1937. A month prior to that time he had developed what to him appeared to be a cold and bronchitis, characterized by cough, yellowish sputum and night sweats. On December 14, 1937, he became nauseated and vomited. At this time, also, he first noted swelling of the entire face and neck. This swelling was worse in the morning upon awakening and disappeared towards evening. It was noted upon examination at this time that the blood pressure was normal, that cardiac size, rate, rhythm and sounds were normal, and that the lungs were clear to percussion and auscultation. Mild jaundice of the skin and sclerae was present. The liver was enlarged to three fingers'-breadth below the costal margin.

Following a diagnosis by his local physician of gall-bladder trouble the patient was given intramuscular injections of calcium gluconate on alternate days over a period of about a week. Although the injections seemed to decrease the amount of swelling temporarily, towards the end of the period of injections the face had become increasingly swelled. This facial edema disappeared after the patient was up and about. Temperature at this time reached a maximum of 101° F. The liver remained palpable, and there was tenderness in the region of the gall-bladder. A flat plate of the abdomen showed no evidence of gall stones, but revealed that the right lobe of the liver was enlarged to the crest of the ilium. Erythrocyte count on November 29 was 3.8 millions of cells, leukocytes 9.3 thousands, and hemoglobin 65 per cent.

valvular involvement may be cases of cardiac tumor, but rarely will they be of the type discussed in this paper.

Hemoptysis, the coughing up of small amounts of blood, when interpreted as the result of rupture of a small blood vessel by excess pressure, in the presence of cyanosis and pulmonary symptoms, should suggest the possibility of increased pressure in the pulmonary system. The epistaxes probably are explainable by rupture of a vessel wall from the increased pressure of chronic passive congestion.

#### SUMMARY

Two cases of idiopathic hemorrhagic sarcoma (Kaposi's disease) involving the heart are reported and discussed, with particular emphasis upon the clinical aspects of the cases. The identical clinical courses of the two cases, when compared with similar cases in the literature, constitute a syndrome which may permit of clinical recognition. The outstanding characteristics of this syndrome are as follows. Onset clinically is that of an acute upper respiratory infection which becomes prolonged to the subacute type. Cough, malaise, weakness, night sweats, sputum (occasionally blood-tinged) and hemoptyses occur at one time or another. Edema of the face, at first transitory, later becomes a most characteristic feature. Cyanosis remains constant for the most part, but increases upon occasion. Temperature elevations reach a maximum of 100 or 101 degrees. Roentgen-ray examination repeated at proper intervals may show the tumor mass in the auricle, with or without accompanying pericardial fluid. The latter, if present, is separated by centrifuging into a sediment of erythrocytes overlain by clear xanthochromic fluid.

*Note:* I am indebted to Drs. Charles W. Hyde and Ross Morris for the opportunity of including their case as the second one in this report.

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hemorrhagic while the central portion was whitish and flesh-like in appearance. The endothelial surface of the tumor was smooth. The tumor was seen to impinge upon the entrance of the vena cava into the auricle and also occluded the tricuspid orifice, the leaflets of which were thin and smooth. The right ventricle, left auricle, and left



FIG. 1. Heart with tumor in right auricle, first case.

ventricle showed no significant abnormality. Microscopic examination of the lung showed marked congestion of the blood vessels with extravasation of blood in several small areas. Pulmonary edema was seen in some regions as was hemorrhagic effusion into the alveoli. There were thrombi in the pulmonary arteries. Sections of the tumor from the auricle revealed large areas of necrosis and hemorrhage interspersed among masses of heterogeneously arranged spindle-shaped cells. In some areas the intact cells were arranged in perivascular fashion. In some areas the appearance suggested new formed granulation tissue with capillary proliferation, while in other areas the tissue appeared neoplastic in nature.

*Case 2.* H. L. C., a 26 year old white male, was admitted to the George Washington University Hospital on November 8, 1937, as a patient of Drs. Charles W.

unchanged. On the next day, February 17, 1938, the patient suddenly went into shock and died before any therapy could be administered.

#### AUTOPSY

The autopsy was performed 15 hours after death. The body was that of a well developed but markedly emaciated white male. The heart weighed 250 gm. and showed brown atrophy. There was generalized arteriosclerosis, remote encephalomalacia of the left basal ganglia and a remote infarct of the spleen. Arteriosclerosis was slight, and there was chronic pulmonary emphysema, passive hyperemia, and edema of the lungs. The adrenals were grossly similar. The right weighed 2.7 gm. and its dimensions were 4.6 by 2 by 0.4 cm. The left weighed 2.5 gm. and its dimensions were 4.5 by 1.7 by 0.6 cm. The shape was normal. On the cut surface, the cortical portion, or what was interpreted as such, had a yellowish-gray color. The intensity of the color varied in portions of the organ. The tissue was definitely firmer than usual. No evidence of postmortem autolysis was discovered. The medulla was carefully searched for, but no gross evidence of the presence of this tissue could be demonstrated. The adrenal arteries revealed some sclerosis, but there was no obstruction or thrombosis. The thyroid, pituitary, pineal, and parathyroid glands were removed for examination. They showed no gross abnormalities. The rest of the organs showed no changes of importance in connection with this case. The heart's blood culture taken at the time of the postmortem examination showed no growth.

Microscopic examination of the adrenals demonstrated the following condition. No medulla was present. Extending throughout the central portion of the gland there was a band of acellular connective tissue. The cortical cells did not show the usual regularity of architecture, but were present in scattered foci or nodules. Some of these nodules showed completely degenerated cortical cells in which only the shadows of the cellular structure could be seen. In other places the cells were still present, but they were swollen and showed small dense nuclei. There were other nodules which originally had been cortical in situation. These now consisted of cholesterol and calcium. A few giant cells of the foreign body type were present. There was no evidence of tuberculosis. The fat stain gave an intensely positive reaction. In the capsule of the gland there were many mononuclear cells filled with brownish-red granules which stained positively for iron. A few contained a yellow pigment which was negative for iron. The arteries showed slight sclerosis.

Microscopic examination of the other organs gave no additional information of importance. In particular, the sections of the glands of internal secretion showed no significant changes.

The diagnosis was: (1) cytotoxic contraction of the adrenals including both the medullary and cortical portions; (2) generalized arteriosclerosis; (3) brown atrophy of the heart; (4) emaciation; (5) encephalomalacia, remote.

#### COMMENT

A death, presumably caused by the use of the salt restriction test in the diagnosis of Addison's disease, increases the evidence that this test is not without danger.

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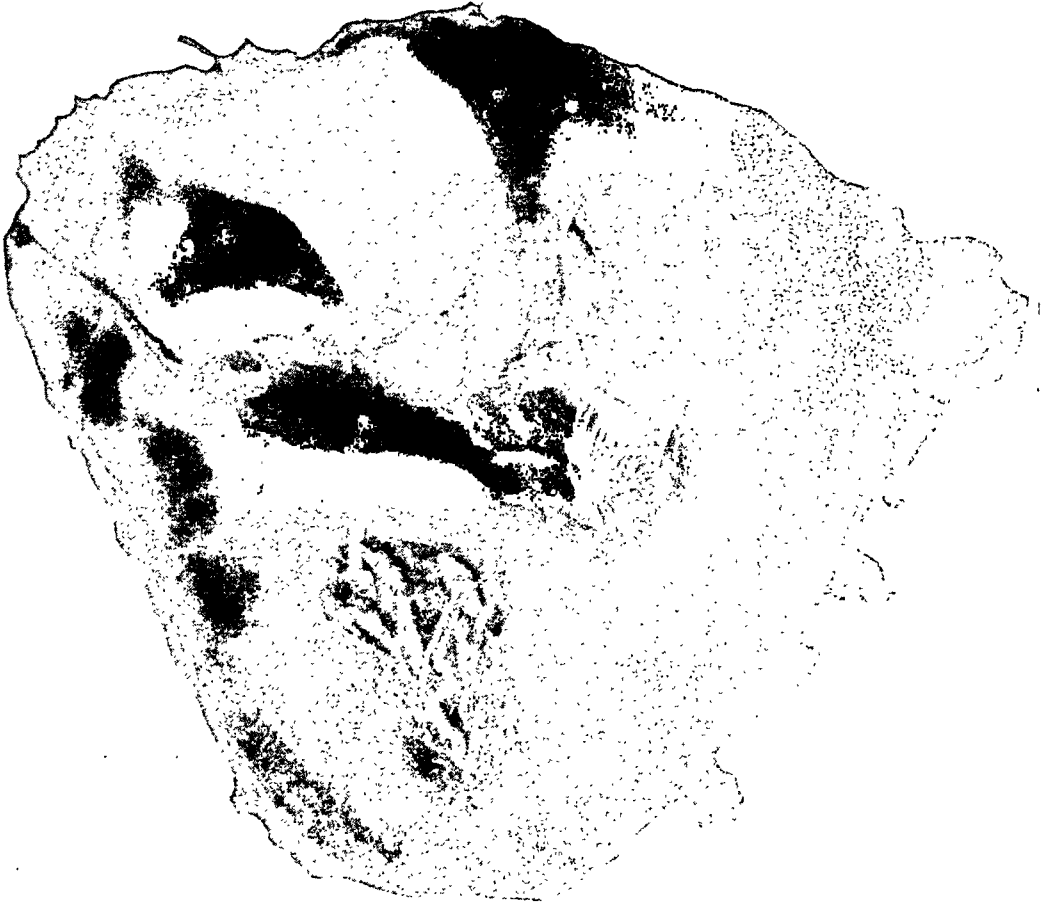


FIG. 2. Heart with adherent pericardium and tumor in right auricle, second case.

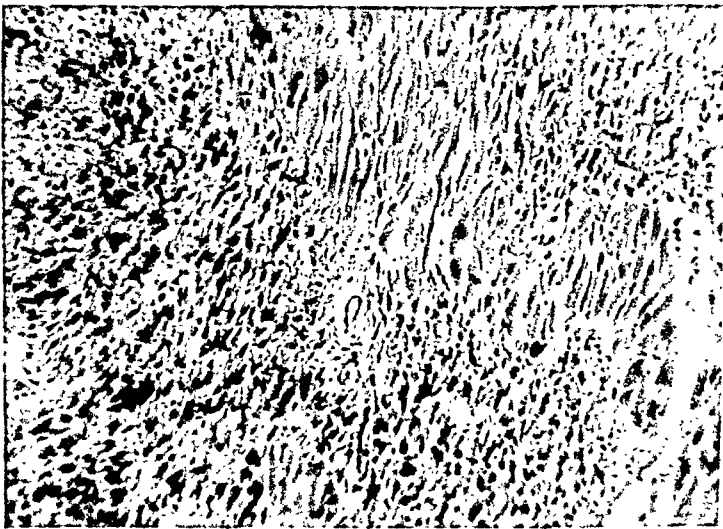


FIG. 3. Section showing invasion of myocardium by tumor, second case.

## ORTHOSTATIC HYPOTENSION: CASE REPORT MENTIONING EFFECTIVE TREATMENT WITH BENZEDRINE SULPHATE\*

By E. S. BREWSTER, M.D., M.Sc. (Med.), *Elkins, West Virginia*

THE condition of orthostatic hypotension, according to a survey of contemporary medical literature, is rare. Since the recognition of this clinical entity in 1925 by Bradbury and Eggleston, who described three cases, probably not more than a total of 50 instances have been published to date. Andrus, in this connection, as recently as September 1937, stated that about 30 cases of this condition had been reported, and Baker, in March 1938, was able to find only 38 instances of this syndrome after a careful search of medical publications. Orthostatic hypotension, however, is probably more common than we suspect, as undoubtedly many cases are not recognized.

### CASE REPORT

W. B., a white female, 67 years of age, was referred to the hospital by her family physician on August 11, 1938, for diagnosis. Her complaints were dizziness and fainting.

The medical history revealed typhoid fever at the age of 12, several attacks of influenza during her later years, and a chronic cystitis during the preceding 5 years.

Her surgical and family histories were irrelevant.

The onset of the present disturbance was in June 1933, with a sudden attack of vertigo soon followed by loss of consciousness, during which she fell down and struck her head. Since then the patient had approximately 200 to 300 experiences of dizziness which were succeeded by syncope. Vertigo alone had occurred so often that she was unable to recall any exact number of attacks. The dizziness and fainting were always worse during the morning and she stated, in this connection, that she invariably felt stronger in the evening. The majority of these attacks took place in her home, but a few proved embarrassing by occurring in public places. She herself noticed that a change in position from the recumbent to either the sitting or standing postures would invariably make her dizzy and often cause her to faint. At this point it is interesting to mention that many of her attacks of syncope had taken place en route from her bed to the bathroom. Experience had taught her that a prone position in bed was the safest.

*Examination.* The patient was an elderly, obese white female, 67 years of age, who was observed lying quietly in bed in the recumbent position. No pain, dyspnea, or discomfort was noted.

The routine admission findings were: pulse, 72 beats per minute; temperature, 98° F. (oral); respirations, 18 per minute; and blood pressure, 124 mm. mercury systolic over 80 mm. diastolic in the recumbent position.

The skin was sallow and somewhat greasy and coarse on palpation. No eruptions or scars were seen.

The eyes presented the following abnormalities. The right pupil was normal, but the left pupil was miotic. Both pupils, however, were round and regular and both responded to light and accommodation normally. Enophthalmos of the left eyeball and a decrease in the left palpebral fissure were observed. Ptosis of the left upper lid was present, and the left upper lid was weaker than the right when elevation was attempted.

\* Received for publication February 13, 1939.

hospital roentgen-ray films had revealed only slight prominence of the right auricle. Upon admission to the hospital a sharp "bulge" seen in the region of the right auricle proved to be, at autopsy, the tumor in the right auricle.

Analysis of the remaining symptoms and physical signs which occurred in the present cases, in their relation to other cases reported in the literature, is as follows.

*Upper Respiratory Tract Infection.* Norton's case was diagnosed upon admission to hospital as bronchopneumonia accompanied by acute toxic myocarditis. The patient reported in the Cabot case developed cough associated with fever and pain in the chest seven months before admission to hospital. The two cases reported here were characterized during the major portion of their illnesses by symptoms of subacute upper respiratory infections. In retrospect, it is obvious that these symptoms had their origin in the atelectatic, congestive, thrombotic and infarctive changes occurring in the pulmonary tissues throughout the clinical course of the disease. Any one of these types of pulmonary involvement is liable to give rise to fever, cough or hemoptysis. When they occur in combinations, with one type of disturbance more prominent at one time and another type at another time, the reason why quiescent intervals and exacerbations occur at various times is obvious.

At the present time it seems impossible by roentgen-ray examination of the lungs to diagnose at an early stage the changes just described. However, there seems no reason why, with improvement in technical methods and increased correlative studies, it should not be possible to diagnose small infarcted and atelectatic areas in the lung tissue. This would be valuable diagnostic evidence in the early stages of the disease.

We wish to emphasize here, therefore, the fact that in cases of neoplasm involving the right auricle the symptoms of respiratory system involvement are probably the outstanding ones during the major portion of the illness. We feel that it is among the group of atypical, prolonged "upper respiratory" cases, with subsequent development into "cardiac" types of cases, that there is offered the greatest possibility for correct clinical diagnosis. In fact, the similarities in the two cases here reported were so striking that, except for the probabilities of two such cases occurring within a period of six weeks being so very remote, the diagnosis of Kaposi's disease involving the heart would have been entertained more seriously than was the case.

When heart block, particularly the complete type, occurs, as is emphasized by Yater, there is considerable likelihood of clinical diagnosis of cardiac involvement. In such cases, however, cardiac involvement ordinarily is secondary to a neoplastic process elsewhere so that lesions in the heart are the result of metastatic involvement. In this rather rare type of primary cardiac involvement the lesion is located near the conducting system and is not a tumor of the auricle.

Cases in which there is variation in the patient's condition and physical signs from the recumbent to sitting posture, or vice versa, also seem likely candidates for cardiac tumors usually of types other than those described herein. The classic type of case giving physical signs which vary with posture is the one of ball valve thrombus. If too much attention is paid to this criterion there is liable to be much confusion with this type of case. Cases with atypical signs of



TABLE I

Position	Time	Blood Pressure	Pulse	Symptoms
Recumbent	3.15 p.m.	110/76	80	
Recumbent	3.16 p.m.	106/74	80	
Sitting	3.16½ p.m.	68/50	80	
Sitting	3.17 p.m.	72/58	82	
Sitting	3.17½ p.m.	82/60	76	
Sitting	3.19 p.m.	82/62	86	
Sitting	3.21 p.m.	82/62	78	Dizzy
Sitting	3.46 p.m.	78/66	80	Very dizzy—felt faint
Supine for 50 min.	4.36 p. m.	106/74	74	Felt better
Sitting	4.37 p.m.	62/50	84	

TABLE II

Position	Time	Blood Pressure	Pulse	Symptoms
Recumbent	After 15 mins.	138/84	80	
Sitting	15 secs. later	78/52	88	
Standing	15 secs. later	60-50/?	*	Dizzy, weak—felt faint

\* Unable to obtain pulse rate because of rapid development of dizziness, weakness, and a sensation of impending faintness.

TABLE III

Position	Time	Blood Pressure	Pulse	Symptoms
Recumbent	After 15 mins.	128/86	82	
Standing	20 secs. later	84/?	84	Dizzy, weak—almost fainted

The diagnosis of orthostatic hypotension is based, therefore, on the following facts: (1) a history of dizziness, and dizziness rapidly succeeded by syncope on assumption of the upright position; (2) immediate severe fall in the systolic blood pressure accompanied by a simultaneous, but usually smaller drop in the diastolic pressure; (3) the unusual stability of the pulse rate despite the marked blood pressure changes; (4) the development of dizziness, weakness, and fainting on sitting up or standing; and (5) the marked symptomatic relief and general improvement produced by benzedrine sulphate.

In regard to diagnosis in this case it is interesting to note that the patient had been hospitalized on four previous occasions because of vertigo and syncope, and in no instance had the correct diagnosis been discovered. The reasons for failure to arrive at an earlier diagnosis in this particular instance are undoubtedly as follows: first, she was uncoöperative in her attitude and refused to stay in the hospitals long enough to permit a careful study of her condition; and second, orthostatic hypotension is a new and rare syndrome and because of its unfamiliarity may easily escape clinical recognition.

*Later Course.* The patient was returned to the care of her referring physician, who was acquainted with the diagnosis, with the advice that she be placed on benzedrine sulphate therapy—one 10 mg. tablet three times a day. He informed me four and a half months after the patient's hospital discharge that she had shown remarkable symptomatic and clinical improvement under the benzedrine sulphate treatment. She is now ambulatory and able to do some of her housework in the morning. In addition, she has not been troubled with fainting, and has experienced only an occasional attack of vertigo since beginning this form of therapy.

## DEATH PRESUMABLY DUE TO THE USE OF THE SALT RESTRICTION TEST IN THE DIAGNOSIS OF ADDISON'S DISEASE\*

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THE use of a low salt diet as a diagnostic test in doubtful cases of Addison's disease was suggested by Harrop and his coworkers<sup>1</sup> in 1933. Two to five days after beginning the restriction of sodium chloride signs of relapse and characteristic concomitant alterations in the blood occur. That the test is dangerous has been recognized. Cortical extract, as well as intravenous salt solution, must be immediately available in event of a serious crisis.

This communication reports a sudden death occurring in a patient with Addison's disease during the period of a salt restriction test. Another report of death, presumably due to the use of the salt restriction test, has been published by Lilienfeld.<sup>2</sup> Since sudden death is common in Addison's disease, Lilienfeld did not think that a direct relationship between the salt restriction and the patient's death could be proved. He pointed out, however, that the use of the salt-free diet must be considered as a hazardous procedure.

### CASE REPORT

W. C., a 51 year old white male, was admitted to Cleveland City Hospital January 7, 1938. His chief complaint was weakness for the past six months. The patient had been in good health until June 1937, when he noticed that his legs were unstable and that he was unable to walk with ease. He tired easily, and finally lassitude became so extreme that he was forced to bed. He had had occasional spells of vomiting, and had noted difficulty in swallowing food and epigastric discomfort after meals.

Examination showed the patient to be normally developed but extremely emaciated and dehydrated. The skin showed no abnormal pigmentation, but there was slight pigmentation of the buccal mucosa. The blood pressure measured in millimeters of mercury never exceeded 85 systolic, and the diastolic value averaged 60. Otherwise physical examination was negative.

The number of erythrocytes and leukocytes and the value for hemoglobin were normal. Urinalysis was negative. The spinal fluid Wassermann test and the blood Kline test were negative. The value of the blood urea nitrogen was 40.6 mg. per 100 c.c. of blood, but this later dropped to 15.1 mg. The value of the blood sugar was 72, of the sodium chloride 429, and of the cholesterol 192 mg. per 100 c.c. of blood. The basal metabolic rate was minus 27 per cent.

Fluoroscopic and film studies of the chest showed the heart to be smaller than normal. Several gastrointestinal series showed no evidence of a pathological process.

Because the case was thought to be not altogether typical of Addison's disease, the patient was placed on a salt-free diet in order to precipitate a crisis and thus establish a definite diagnosis. At the end of the customary six-day period there was no change in the patient's condition, and it was decided to continue the test a few days more. On the seventh day the patient was more lethargic than usual and did not take his food well. The blood pressure at that time was 80 mm. Hg systolic and 60 diastolic. The following day the patient refused food, but otherwise his condition seemed

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## TREATMENT

Vasoconstrictor drugs are the most efficient agents capable of affording symptomatic relief in postural hypotension. The drugs of choice in this group are ephedrine sulphate, benzedrine sulphate, and neosynephrine hydrochloride. These drugs act by elevating the blood pressure through a prolonged vasopressor effect on the splanchnic arterioles. In this way a sufficiently high systolic blood pressure can be maintained to insure the hypotensive individual a considerable amount of physical freedom in the upright position. Successful treatment of orthostatic hypotension by ephedrine was reported in one instance by Ghrist and Brown in 1928. Ephedrine was most beneficial in their case when given every hour in 25 mg. doses. This dosage was later reduced to two or three capsules of 50 mg. each a day, and their patient was able to manage very well on this decreased amount. Korns and Randall, in January 1937, were the first to describe the beneficial value of benzedrine sulphate in one case, and three months later Davis and Shumway-Davis confirmed this work and published an account of effective therapy with benzedrine sulphate in two cases of their own. Baker, in 1938, reported the fourth case of orthostatic hypotension which has been benefited by benzedrine sulphate administration. There are some instances of postural hypotension, however, which do not respond favorably to ephedrine, benzedrine, or combined ephedrine and benzedrine types of treatment. Capaccio and Donald, in 1938, described such an instance in which they were successful in securing symptomatic relief by the oral use of neosynephrine hydrochloride in daily doses of 150 mg., finally reduced to 60 mg. Neosynephrine is a synthetic drug which is very closely related to epinephrine, but differs from epinephrine in that its vasopressor action is greatly prolonged. Neosynephrine may ultimately replace ephedrine sulphate in the treatment of orthostatic hypotension since the use of neosynephrine apparently does not produce the unpleasant secondary effects of cardiac arrhythmia, palpitations, nervousness, giddiness, and insomnia, which frequently follow the administration of epinephrine or ephedrine.

## SUMMARY

1. A case of orthostatic hypotension occurring in a white woman 67 years of age has been described.

2. Symptomatic relief and general improvement occurred promptly in this patient following the oral administration of 10 mg. of benzedrine sulphate three times a day.

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## COBRA VENOM INEFFECTIVE IN TWO CASES \*

By WINGATE M. JOHNSON, M.D., F.A.C.P., *Winston-Salem, North Carolina*

IN THE ANNALS OF INTERNAL MEDICINE for April 1938, Dr. David I. Macht presented an intriguing article on the use of cobra venom for the relief of persistent pain. The impression was left with this reader, at least, that cobra venom was usually so effective in relieving persistent pain that it could be substituted for opium derivatives, and that in doses at intervals of two to four days it would keep a patient as comfortable as would several doses a day of morphine.

Since the only way properly to evaluate a new, or newly discovered, drug clinically is for enough practitioners to use it and compare results, and since I have seen no comments on Dr. Macht's article, I am submitting briefly my experience with cobra venom in two cases.

## CASE REPORTS

*Case 1.* A 15 year old white girl two years ago had her right leg amputated above the knee because of sarcoma. In spite of roentgen-ray treatments subsequent to the operation the growth metastasized to the spine, causing constant pain. At the time the cobra venom was begun, she was taking  $\frac{1}{8}$  grain of morphine three times a day. The venom was given according to directions, 0.5 c.c. hypodermically the first day, daily doses of 1.0 c.c. for three days, then on alternate days for two more weeks. In spite of the venom morphine had to be given in increasing doses and at more frequent intervals. The verdict of all who were in attendance on the case was that there was apparently no appreciable effect from the cobra venom.

*Case 2.* A very intelligent and coöperative white male, 54 years old, had been confined to bed for more than two years with severe coronary disease. In spite of bed rest he was having a number of anginal attacks daily. When the cobra venom was first begun he was rather enthusiastic about the relief he thought it afforded, but this enthusiasm soon began to wane. When the ninth dose was due I found that the neck of the ampoule was cracked, so took advantage of this opportunity to give him 1.0 c.c. of boiled water instead of the venom. On my next visit he reported that he had had the most comfortable period of any since the treatment was begun. I never told him of the deception, but agreed to his request that the twelfth dose be omitted, as he had decided that all the relief he thought he had obtained at first was mental.

Unfavorable results, as well as optimistic ones, should be made known. Certainly these two cases seemed "made to order" for treatment by cobra venom, but in both it proved absolutely useless, except for the brief period of psychic effect in the second case.

\* Received for publication December 9, 1938.

increased up to the maximum, which was 0.75 gm. every three hours. At no time during the administration of the drug was there the slightest toxic effect noted.

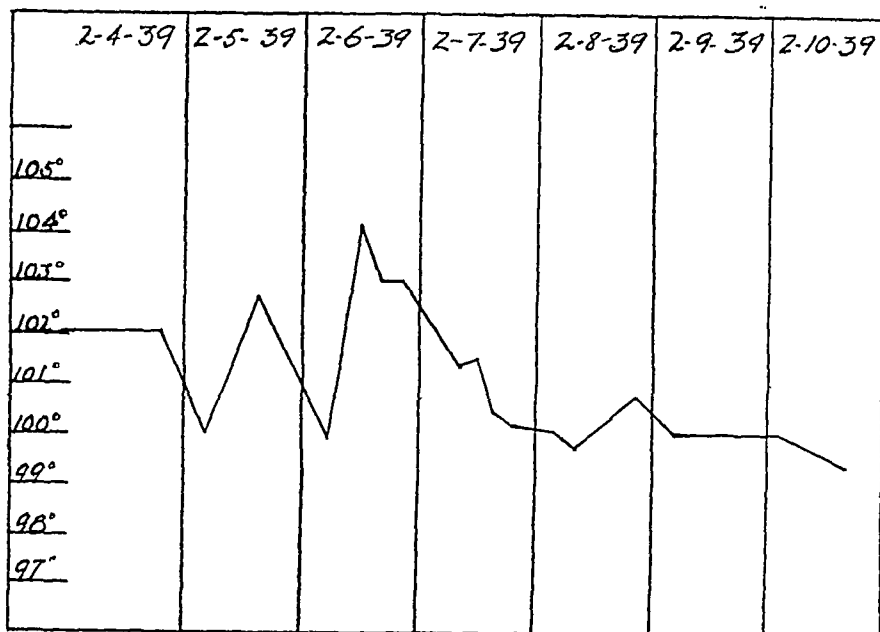


FIG. 1. The temperature curve of a case of Pfeiffer meningitis treated with sulfapyridine.

Figure 1 shows the temperature curve of the patient. Within 24 hours from the time the drug was started the temperature showed a continuous drop, and within 36 hours the temperature reached normal limits. At no time after this during the 20 days stay in the Hospital did the rectal temperature go above 100 degrees.

TABLE II  
Examinations of the Spinal Fluid

Date	Cell Count	Smear	Culture	Differential Cell Count
2/ 4/39	3,050	Many gram neg. bacilli	Pfeiffer bacilli	90% neutrophils 10% lymphocytes
2/ 9/39	200	No organisms	No growth	90% neutrophils 10% lymphocytes
2/13/39	30	No organisms	No growth	
2/20/39	31	No organisms	No growth	80% neutrophils 20% lymphocytes

On February 9 a spinal puncture was done. The cell count was 200, and no organisms were found in either the smear or the culture. At this time the neck rigidity had subsided considerably and the Brudzinski sign was absent. From that day forward the clinical course was uneventful, being marked by gradual recovery.

Fundus examination revealed moderate thickening, beading, and tortuosity of the retinal arteries in both eyes. The optic discs were normal and there was no evidence of retinal hemorrhage either old or recent.

The external auditory canals and drums of both ears showed no abnormalities. Hearing, as determined by the watch test, was equal on both sides and showed no impairment.

The patient was edentulous. The tonsils, although atrophic, showed evidence of mild chronic inflammation. The throat was normal and the uvula showed no deviation. The thyroid gland was slightly enlarged.

The superficial lymph glands were not palpable.

The chest was normal on inspection, palpation, and percussion, but auscultation revealed the presence of a few transient dry crackling râles heard posteriorly over the left apex, left base, and over the lower left axilla. The breasts were normal.

The apex beat of the heart was neither visible nor palpable. On percussion the position of the left cardiac border (M. L. 12 cm.) indicated slight enlargement. The cardiac sounds were of fair quality and  $A_2$  was louder than  $P_2$ . No murmurs and no arrhythmias were heard. The blood pressure was 124 mm. mercury systolic over 80 mm. diastolic in the recumbent position.

The abdomen was slightly distended and a tympanitic note was elicited by percussion. The striae of previous pregnancies were visible. No masses and no tenderness were discovered on palpation.

The legs and thighs contained many superficial varicose veins, a few of which were thrombosed.

The peripheral arteries—radial, brachial, and temporal—were thickened and slightly tortuous.

Cystocele and rectocele were found on vaginal inspection. Rectal examination was negative.

Neurological examination showed that the superficial and deep reflexes were normal with the exception of the Romberg sign, which was positive. On standing the patient complained of dizziness and a sensation of impending faintness, and would have collapsed had she not been permitted to lie down. Pain and temperature sensations were intact and there was no recollection of any tingling, numbness, or paresthesia affecting the extremities. The grip of both hands was strong and the muscles of the arms and legs revealed no weakness nor atrophy. The speech showed no abnormalities, but a coarse generalized involuntary tremor was observed.

The mentality was clear and memory for past events was fairly good. There was no disorientation in regard to time, place, or person.

The impressions gathered from the physical examination were: (1) Horner's syndrome—left; (2) moderate arteriosclerosis of the retinal arteries; (3) moderate arteriosclerosis of the peripheral arteries; (4) adentia of both jaws; (5) mild chronic tonsillitis; (6) superficial varicose veins of the lower extremities; (7) cystocele; and (8) rectocele.

*Laboratory.* Two urinalyses were done which were normal. The hemoglobin was 82 per cent (Sahli method—17.3 grams of Hb. equals 100 per cent); there were 4,080,000 red blood cells, and 7,300 white blood cells per cu. mm. The blood Kahn test was negative.

*Diagnosis.* The history in this case was of extreme importance because it furnished the diagnostic clues. The story of vertigo and syncope following a change from the recumbent to the sitting or standing positions was suggestive of orthostatic hypotension. Special blood pressure and pulse examinations, with particular reference to changes in the patient's posture, confirmed this diagnosis. These examinations are tabulated as follows:

## EDITORIAL

### *MEDICAL CARE IN HANDICAPPED RURAL AREAS*

MEDICAL care, adequate for the standards of the period, could be given in rural areas 40 years ago by general practitioners, in the home and office with occasional transferral of a difficult problem to the city. Advancing standards led to the widespread construction of rural hospitals, at first in the larger towns and then in smaller communities. Specialization in medical practice also has spread, first to the smaller cities and then to the towns, especially in certain sections of the country. Organized programs of preventive medicine have been extended into the rural areas.

Medicine, both preventive and curative, is a rapidly advancing science. Full advantage of its benefits can be obtained in rural districts only if in addition to well trained and equipped general practitioners there are available adequate local hospital facilities, an active health program, feasible arrangements for consultation with specialists, and a system whereby certain patients can be transferred for study or treatment to larger medical centers. Fortunately, in many rural regions these conditions obtain. The level of medical care in the more prosperous country areas is steadily rising.

There are, however, rural areas in many parts of the United States in which the picture as to medical care is far less encouraging. It is to be expected that wilderness areas with widely scattered sparse populations will be backward in medical care, but it is to well populated areas that we refer. Poverty of the population and remoteness from a medical center are two factors which combine in many instances to bring about a stationary or even a falling level of medical care.

The level of medical care in such an area cannot be determined with any accuracy by available statistics on the number of physicians, hospital beds and public health clinic visits, etc., though these figures yield a certain amount of information. Such quantitative measures are, however, deceptive. A qualitative survey on the ground is much more instructive.

In a remote and impoverished area of the country the number of physicians may be found to be quite adequate, and is only rarely grossly inadequate unless the country is very sparsely settled. The reason appears to be that in the first decade of the century the annual output of physicians was very large and was composed predominantly of men trained only for general practice. Even the remote areas of low economic status were well supplied. With the coming of automobiles and better roads, increasing a physician's range, the survivors of that period still constitute numerically an adequate number of physicians. If one studies, however, the number of young men going into practice in such areas the impression is gained that from now on, unless this number increases, there will be a growing scarcity of physicians.

## ETIOLOGICAL CONSIDERATION OF ORTHOSTATIC HYPOTENSION

This syndrome is regarded essentially as an imbalance of the autonomic nervous system in which both the sympathetic and parasympathetic divisions are affected. Two prominent features which indicate involvement of the sympathetic division are: (1) a peculiar diminution of reflex splanchnic vasoconstriction, which normally stabilizes the changes in blood volume in the dependent portions of the body when the upright position is assumed; and (2) a deficiency or absence of normal sweating which may be either localized or generalized in extent. Disturbance of the parasympathetic division is recognized by the abnormal maintenance of a comparatively stable pulse rate despite marked blood pressure fluctuations when postural changes are made. This phenomenon is caused by a failure of the vagus nerve to respond normally to blood pressure variations.

Bradbury and Eggleston in 1925 stated that the pathology was localized in the myoneural junctions of the splanchnic vessels and that true paralysis occurred. Ghrist and Brown, in 1927, while agreeing with Bradbury and Eggleston on the myoneural junction as the site of the trouble, considered the disturbance one of hypotonia rather than paralysis, and suggested, in addition, that this condition might be secondary to some primary cause. A comprehensive explanation of the vascular changes occurring in postural hypotension was reported by Ellis and Haynes in 1936. These investigators concluded that the syndrome was featured by: (1) a loss of reflex vasoconstriction of the splanchnic arterioles upon assumption of the upright position; and (2) by a loss of the reflex increase in the pulse rate on sitting or standing. The symptoms of weakness, vertigo, and syncope are, therefore, better understood after realizing that the simultaneous occurrence of three factors, i.e., severe stasis of blood in the splanchnic area, slow pulse rate, and abnormally low blood pressure, leads to a rapid and marked cerebral anemia when the upright position is attempted.

Many instances of orthostatic hypotension are undoubtedly idiopathic. Recent reports indicate, however, that an increasing number are associated with various pathologic conditions affecting the central nervous system. Ellis and Haynes reported in 1936 that 10 of 17 successive cases of *tabes dorsalis* showed characteristic falls in systolic and diastolic blood pressures in the sitting and standing postures. Orthostatic hypotension was also described in two instances of *myasthenia gravis* by MacLean and Horton in 1937. Other pathological states of the central nervous system found in association with postural hypotension are traumatic *hematomyelia*, *syringomyelia*, and a peculiar patchy type of *arteriosclerotic degeneration* widely disseminated throughout the entire central nervous system. In addition, according to Brown, Craig, and Adson, in 1935, an "acquired" form of orthostatic hypotension has occurred in some of their hypertensive patients following anterior rhizotomy of the lower thoracic and lumbar spinal nerves. Due to the frequent association of postural hypotension with certain pathological and surgical conditions of the central nervous system the question arises: is this association merely a coincidence or are these disturbances of the central nervous system the basic causes of the hypotension.



The physician must see a chance for a reasonable livelihood in the region in which he works. If he were assured of receiving an adequate recompense for the care of the indigent and of the medically indigent this requirement could be met.

The facilities for practicing the type of medicine he has been trained for and of further developing his abilities must be furnished him. The raising of the standards of county hospitals and the physician's participation in well run special clinics will go a long way towards this goal.

A means of keeping contact with the advances in medicine must be made available to the rural physician. There are many devices for this purpose but none perhaps is sounder than the principle employed in medical schools. There, participation of the student in a program for the care of the indigent under his medical instructors is the basis of clinical teaching. Regular consultation clinics under teaching specialists as a part of the program for medical care of indigents in the rural area would have the same practical instructional value.

The meeting of these basic requirements need not involve "socialized medicine" nor anything detrimental to the ideals of the medical profession. It does involve a determined and coöperative effort on the part of all those chiefly concerned in medical care—the lay public, the practicing medical profession, the health department, the welfare department and others. These must combine to obtain for such handicapped areas the financial help which is necessary to establish a better level of medical care and to devise the medical care program. Only if the medical profession takes an active part in such a coöperative effort is it likely to find embodied in such a program the sound principles of medical care which its experience has demonstrated to be essential.

M. C. P.

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8. KORN, H. M., and RANDALL, W. L.: Orthostatic hypotension treated with benzedrine, *Am. Heart Jr.*, 1937, xiii, 114-118.
9. DAVIS, P. L., and SHUMWAY-DAVIS, MARGARET: Orthostatic hypotension: The treatment of two cases with benzedrine sulphate, *Jr. Am. Med. Assoc.*, 1937, cviii, 1247-1249.
10. CAPACCIO, G. D., and DONALD, C. J.: Orthostatic hypotension: report of a case treated with neosynephrine hydrochloride, *Jr. Am. Med. Assoc.*, 1938, cx, 1180-1182.

## PFEIFFER BACILLUS MENINGITIS; THE CURE OF A CASE WITH SULFAPYRIDINE\*

By C. C. McLEAN, M.D., F.A.C.P., ARTHUR W. WOODS, M.D., and  
H. H. HENDERSON, M.D., *Birmingham, Alabama*

DUE to the fact that the results in this particular patient were so spectacular and that the dosage of the drug given was somewhat larger than is generally recommended, it was thought that a report of this case might be of interest.

### CASE REPORT

L. H., colored male, 30 months of age, weight 32½ pounds, was admitted to Hillman Hospital at 9:45 p.m., February 4, 1939, with a history of fever, vomiting, and headache of five days' duration. Entrance examination revealed a rectal temperature of 102° F., positive Kernig and Brudzinski signs, increased tendon reflexes, and a stuporous mental condition. The spinal fluid was obtained under slightly increased pressure; it was cloudy, and the cell count was 3,050 (90 per cent neutrophiles). Many gram negative bacilli and a few questionable gram negative diplococci were seen on smear. The culture of this fluid was reported as having an abundant growth of Pfeiffer's bacilli. The white blood count was 24,500, neutrophiles 82 per cent.

On February 5, 1939, at 6:00 p.m. sulfapyridine therapy was started.

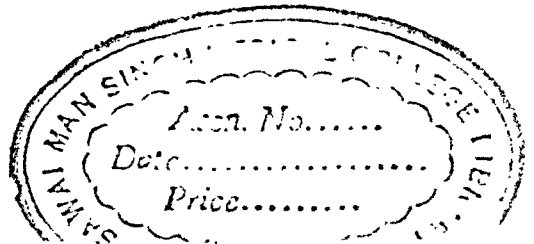
TABLE I  
Dosage of Sulfapyridine †

Dosage	Interval	Time
0.25 gm.....	3 hours	Feb. 5 to Feb. 7
0.5 gm.....	3 hours	Feb. 7 to Feb. 8
0.75 gm.....	3 hours	Feb. 8 to Feb. 10
0.5 gm.....	6 hours	Feb. 10 to Feb. 17
0.5 gm.....	12 hours	Feb. 17 to Feb. 20
0.5 gm.....	24 hours	Feb. 20 to Feb. 23

† Dagenan, 2-Sulfanilyl Aminopyridine, MB-693 (Merck & Co.).

Table 1 shows dosage, interval and the time the drug was given. The patient was first given 0.25 gm. every three hours, the size of the dose gradually being

\* Received for publication April 24, 1939.



The first chief division is that of general therapy, which contains adequate, though summary, subsections on the use of drugs, gases, vaccines and sera, organo-therapy, parenteral fluid administration, transfusion, diet, physiotherapy, occupational therapy, climate, etc. The excellent and sane discussion of various modes of physiotherapy is valuable and the whole section is very readable. The section on drugs contains a great deal of valuable information as to their uses and contraindications in brief and clear form.

It is not possible to review in detail the sections on general diseases, infectious diseases, and diseases of the various systems of the body. The real value of such a system as well as its weak points can become evident only through a number of months of continuous use as a reference in connection with the daily problems of practice. In so using it for a briefer period on numerous occasions the reviewer has been impressed with the high level of the contributions it contains. Moreover there is a minimum of extraneous matter and an evident attempt to give succinct practical descriptions of the therapy advocated. In most articles there is a touch of authority acquired by extensive personal experience which inspires confidence. It will be a valuable work for all medical men—students, general practitioners, and internists—and should serve as a standard reference for many years. The highest level of modern medical therapy has nowhere been more adequately presented.

M. C. P.

*Some Fundamental Aspects of the Cancer Problem.* Edited by HENRY BALDWIN WARD. 248 pages; 27 × 19 cm. The Science Press, New York City. 1937. Price, \$2.00 (paper); \$2.50 (cloth).

This book is composed of 30 papers read before the Atlantic City meeting of the American Association for the Advancement of Science, December 29, 1936 to January 1, 1937. These papers are put into five groups as follows:

1. Heredity and constitutional factors.
2. Induction, stimulation and inhibition of tumorous growths.
3. Metabolism of cancer tissue.
4. Radiation.
5. General discussion of cancer problems.

The authors of these articles are world-renowned scientists who have done much original research in their various fields. Among them are Maud Slye, C. C. Little, Francis Carter Wood, G. Failla, Charles Geschickter, et al. In the brief space allotted to this review, one can not begin to cover the subjects treated. The book furnishes a wealth of material and should be on the shelves of every person interested in cancer. So many fundamentals of the cancer problem are considered that the book becomes a ready reference volume for the cancer worker.

G. E. W.

*Beyond the Clinical Frontiers.* By EDWARD A. STRECKER, M.D. 210 pages; 21 × 14 cm. W. W. Norton & Co., New York City. 1940. Price, \$2.00.

This 200 page volume represents Dr. Strecker's Thomas W. Salmon Memorial Lectures. It is essentially an application of lessons learned from the study of individual psychiatric patients and the problems of mass psychology, and a discussion of what the principles of mental hygiene have to offer in dealing with the "crowd-mind."

Dr. Strecker begins by considering the development of psychoneurotic and psychotic conditions as a retreat from reality. He takes up various commonly used methods of evading the ordinary responsibilities of living, points out some of the

TABLE III  
Examinations of the Blood

Date	Hb.	R.B.C.	W.B.C.	Polys.	L. Lymphs.	S. Lymphs.	Remarks
2/ 5/39	62%	3,370,000	24,500	82%	1%	17%	Wassermann test neg. Blood culture: no growth
2/ 9/39	52%	3,120,000	22,450	79%	2%	19%	
2/11/39			17,400	32%	0	68%	
2/15/39	68%	3,530,000	9,600	56%	0	44%	

On February 13 a spinal puncture was done; the cell count was 30 and no organisms were found in the smear or in the culture. On February 15 the white blood count was 9,600, neutrophils 56 per cent.

# COLLEGE NEWS NOTES

## GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following reprints by members of the College:

Dr. William Wallace Alexander, F.A.C.P., Florence, Ala.—1 reprint;  
Dr. C. Charles Burlingame, F.A.C.P., Hartford, Conn.—1 reprint;  
Dr. Hervey M. Cleckley (Associate), Augusta, Ga.—3 reprints;  
Dr. William E. Costolow, F.A.C.P., Los Angeles, Calif.—4 reprints;  
Dr. Joseph F. Elward (Associate), Washington, D. C.—7 reprints;  
Dr. Archie L. Gleason, F.A.C.P., Great Falls, Mont.—1 reprint;  
Dr. Marion Douglas Hargrove, F.A.C.P., Shreveport, La.—1 reprint;  
Dr. Howard L. Hull, F.A.C.P., Yakima, Wash.—1 reprint;  
Dr. Abraham E. Jaffin, F.A.C.P., Jersey City, N. J.—3 reprints;  
Dr. Bert F. Keltz, F.A.C.P., Oklahoma City, Okla.—1 reprint;  
Dr. Lionel S. Luton, F.A.C.P., St. Louis, Mo.—3 reprints;  
Dr. Frank B. Marsh (Associate), Salisbury, N. C.—2 reprints;  
Major Horace P. Marvin, F.A.C.P. (MC), U. S. A.—1 reprint;  
Dr. J. R. S. Mays (Associate), Baltimore, Md.—1 reprint;  
Dr. William Gerry Morgan, M.A.C.P., Washington, D. C.—38 reprints;  
Dr. Hubert M. Parker (Associate), Kansas City, Mo.—2 reprints;  
Dr. Arthur J. Patek, F.A.C.P., Milwaukee, Wis.—1 reprint;  
Dr. Albert E. Russell, F.A.C.P., New York, N. Y.—2 reprints;  
Dr. Louis H. Sigler (Associate), Brooklyn, N. Y.—1 reprint;  
Dr. Albert Soiland, F.A.C.P., Los Angeles, Calif.—4 reprints;  
Dr. Abraham Trasoff (Associate), Philadelphia, Pa.—10 reprints;  
Dr. Charles F. Warren (Associate), Brooklyn, N. Y.—1 reprint;  
Dr. Samuel Arthur Weisman, F.A.C.P., Minneapolis, Min.—2 reprints;  
Dr. Howard F. West, F.A.C.P., Los Angeles, Calif.—3 reprints.

## AMERICAN COLLEGE OF PHYSICIANS COÖPERATING WITH SURGEONS GENERAL OF THE PUBLIC SERVICES

President James D. Bruce, with the approval of the Executive Committee of the American College of Physicians, during June appointed a Preparedness Committee consisting of:

Dr. James E. Paullin, F.A.C.P., Atlanta, *Chairman*  
Dr. Roger I. Lee, F.A.C.P., Boston  
Dr. Edward L. Bortz, F.A.C.P., Philadelphia  
Dr. Ernest E. Irons, F.A.C.P., Chicago

to coöperate with the Surgeons General of the Army, Navy and Public Health Service of the United States, and with the Preparedness Committee of the American Medical Association in making available the services of the College to these Government agencies. Dr. Paullin is also a member of the Committee on Medical Preparedness of the American Medical Association.

In response to informal requests from the Surgeons General of the Army and Navy, the National Research Council organized the Division of Medical Sciences, of which the Committee on Medicine is a part. The Committee of the American College of Physicians is allied with the Committee on Medicine, of which Dr. Russell Wilder, F.A.C.P., Rochester, is chairman.

This older group of men who have practiced their profession at a distance from medical centers in a population of low economic level have not as a class been able to keep abreast of many important advances in medicine and have lacked facilities for the application of many new measures of which they did gain knowledge.

The hospitals in such areas, although serving a purpose, are often extremely inadequate as to the facilities they afford. Numerically they may be sufficient, but many are merely old residences converted to hospital purposes and lacking in proper laboratory, roentgenological, nursing and consultant services. Public support from local sources for the medical care of the indigent is apt to be scant in these areas and the number of medically indigent is large. Care of such cases is a heavy burden upon the physician's resources of time and strength and often of money, for he frequently supplies the medicines. The care he can thus give is often restricted to emergency care.

Of course the low level of medical care in the regions referred to is only one evidence of their economic, educational, and social backwardness. There is usually a definite lack of awareness in the average citizen living under these conditions of the advantages to be gained by better medical care and an apathy which discourages those who attempt to improve conditions.

As the number of physicians decreases in such an area it becomes evident to all, however, that efforts to replace them must be made, for no matter how ignorant of the standards of medicine a farm laborer, a fisherman or a woodsman may be he knows he needs a doctor's help for himself and his family in illness. There is a growing demand on the medical schools for practitioners for these less favored regions.

The young physician completing his internship hears of the requests and perhaps investigates. He finds that there is a bare living to be made from paid practice. He learns that he will have to assume, especially as a younger man, a crushing load of free work. He has been trained to employ all the facilities of a hospital, but in the territory which needs him there is no hospital worthy of the name. His progress has been aided by constant commingling with men whose special knowledge is his for the asking, but in this remote area it will be only through reading that he can enlarge his knowledge; and there will probably be little time or energy left for reading. Finally he feels that if he spends as much as five years in such practice, while learning much from experience he will nevertheless have lost so many skills from disuse and failed to learn so many new ones that it will be hard ever to break away and compete with other physicians in a large town or city. To a man who has spent three or four years in college, four years in the medical school and at least a year in a hospital the practice of medicine in a remote and unprosperous rural area has little indeed to offer.

There have been many actual attempts at a solution of this problem and even more theoretical solutions offered. None will be proposed here but certain conditions which must be met may be outlined.

Dr. Dwight L. Wilbur, F.A.C.P.

Dr. James S. McLester, F.A.C.P.

Dr. Norman Jolliffe, F.A.C.P.

*Diseases of Metabolism*

Dr. James H. Means, F.A.C.P., *Chairman*

(Personnel to be selected)

*Therapeutics*

Dr. O. H. Perry Pepper, F.A.C.P., *Chairman*

Dr. Hugh J. Morgan, F.A.C.P.

(Others to be selected)

*Clinical Investigation*

Dr. Eugene F. DuBois, F.A.C.P., *Chairman*

(Personnel to be selected)

It is understood that the American Medical Association, through its Committee on Medical Preparedness, will provide the Governmental Services with the listing of United States physicians, together with their various qualifications, fields of specialty, etc.

SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

The following Boards have announced schedules of their examinations as follows: For further details and application forms communicate with the respective secretaries.

AMERICAN BOARD OF INTERNAL

MEDICINE:

William S. Middleton, M.D.,

Secretary

1301 University Avenue

Madison, Wis.

Written Examination, October 21, 1940.

Oral Examination, Philadelphia, December, 1940.

Written Examination, February 17, 1941.

Oral Examination, Boston, April, 1941, in connection with meeting of the American College of Physicians.

Oral Examination, Cleveland, June, 1941, in connection with meeting of the American Medical Association.

AMERICAN BOARD OF DERMATOLOGY AND

SYPHILOLOGY:

C. Guy Lane, M.D., Secretary

416 Marlboro Street

Boston, Mass.

Written Examination, October 28, 1940.

Oral Examination, Chicago, December 6-7, 1940.

Applicants in Group B take both the written and oral examinations; applicants in Group A take the oral examination only.

AMERICAN BOARD OF PSYCHIATRY AND

NEUROLOGY:

Walter Freeman, M.D., Secretary

1028 Connecticut Ave., N. W.

Washington, D. C.

New York City, December 18-19, 1940.

AMERICAN BOARD OF RADIOLOGY:

B. R. Kirklin, M.D., Secretary

102 Second Ave., S. W.

Rochester, Minn.

Boston, September 26-29, 1940.

Cleveland, June, 1941, at meeting of American Medical Association.

## REVIEWS

*Clinical Diabetes Mellitus and Hyperinsulinism.* By RUSSELL M. WILDER, M.D., Ph.D., F.A.C.P. 459 pages; 24 × 16 cm. W. B. Saunders Co., Philadelphia. 1940. Price, \$6.00.

The author, who for the past 25 years has devoted the major portion of his time to the subject of diabetes, here presents most detailed clinical considerations of this disease.

The theory of carbohydrate metabolism, physiology and pathology of diabetes are presented only briefly. Liberal use of footnotes, a practice rather rare in medical literature, has been employed. For this feature the author is to be complimented. In this way contributory material is added without disturbing the main idea or thought.

Throughout the entire monograph the author freely states his own personal experiences and conclusions but gives due recognition to other workers who possess differing ideas. At the end of each of the 26 chapters extensive and complete references are given, thus greatly increasing the value of the book for those most interested in the subject.

The chapters on infection, surgery in diabetes, pregnancy, diseases of the thyroid and heart disease complicating diabetes are most outstanding.

The author's ideas, especially in respect to the proper diabetic diet and the treatment of diabetic acidosis (coma), are somewhat open for discussion.

The last four chapters are devoted to a most complete and careful review of the subject of hyperinsulinism—"the clinical opposite of diabetes."

This monograph is a most valuable contribution to the interesting subject of diabetes and is unreservedly recommended to the student and practitioner of medicine.  
J. S. E.

*Modern Medical Therapy in General Practice.* Edited by DAVID PRESWICK BARR. 3 volumes. 3781 pages; 18 × 26 cm. The Williams and Wilkins Company, Baltimore. 1940. Price, 3 volumes, \$35.00.

This important addition to the literature on therapy has appeared at a fortunate time to meet a real need. The advances in therapy have been so rapid in recent years and have occurred in so many divisions of medical practice that a system written by a large group of men, each covering the field of his special interest, saves the practitioner a great deal of research into the journal literature.

The selection of authors appears to have been very fortunate and their coöperation with the Editor, for which he thanks them in his preface, must have been unusually prompt, for all the sections reviewed appear to have included the very latest material to the date of publication. This must mean that all their labors were brought to a conclusion within a period of relatively few months—really an extraordinary achievement and one which adds greatly to the value of these volumes.

The amount of space allocated to various subjects has been influenced, the Editor tells us, by the purpose of presenting in detail those therapeutic methods which are adapted to use in general medical practice and only in outline such subjects as radiation therapy or artificially induced fever. On the whole, the length of the work (3 volumes, 3560 pages) has made it possible to give adequate space for a fairly detailed discussion of therapy in medical conditions. Here and there it appears that the length of the articles is not always proportionate to their importance. Thirty-four pages are made to suffice for the treatment of pulmonary tuberculosis, whereas fifteen are required for thrombo-angiitis obliterans. Only seven pages are given to the important subject of blood transfusions, whereas dietotherapy is discussed for 178 pages.



Dr. John R. S. Mays (Associate) resigned May 16, 1940, from the staff of the Milledgeville (Georgia) State Hospital to become Senior Assistant Physician in Psychiatry at the Spring Grove State Hospital, Baltimore, Md.

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Dr. Milton Samuel Sacks (Associate), Baltimore, has been appointed Associate in Medicine and Head of the Department of Clinical Pathology at the University of Maryland School of Medicine as of October 1, 1940.

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Dr. W. Bernard Kinlaw, F.A.C.P., Elmira, N. Y., addressed the Chemung County Medical Society recently on "Discussion of Differential Diagnosis of Hypertension."

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The Eighth Councilor District Meeting of the Medical Society of the State of Pennsylvania was held in Warren, Pa., June 5, 1940. At the morning session Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, Secretary of the Medical Society of the State of Pennsylvania, gave a talk entitled "On This Rock." The following members of the College presented papers during the afternoon scientific session:

Dr. Belford C. Blaine (Associate), Pottsville, Pa.—"Primer on the Simplified Treatment of Diabetes";

Dr. George Booth, F.A.C.P., Pittsburgh, Pa.—"Childhood Diabetes and Its Problems";

Dr. Frank A. Evans, F.A.C.P., Pittsburgh, Pa.—"Management of Diabetes and Its Emergencies."

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Among those who participated in the recent postgraduate course in cardiovascular disease for medical officers of the Veterans Administration, given at Hines, Ill., were:

Dr. James G. Carr, F.A.C.P., Chicago—"Arteriosclerotic Heart Disease";

Dr. Andrew C. Ivy, F.A.C.P., Chicago—"Physiological Aspects of Hypertension."

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Dr. Henry Field Smyth, F.A.C.P., Philadelphia, Assistant Professor of Industrial Hygiene at the University of Pennsylvania School of Medicine, recently received the second annual award of the Pennsylvania Public Health Association for outstanding achievements in public health.

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Dr. James E. Paullin, F.A.C.P., Atlanta, Ga., addressed a recent meeting of the Columbia (South Carolina) Medical Society on "Congestive Heart Failure."

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At a recent meeting of the Greenville County Medical Society, Greenville, S. C., Dr. Eugene M. Landis, F.A.C.P., University, Va., presented a paper on "Pathogenesis and Treatment of Edema," and Dr. Staige D. Blackford (Associate), University, Va., presented a paper on "Spontaneous Pneumothorax."

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Recently, Dr. Edward C. Rosenow (Associate), addressed the Pierce County (Washington) Medical Society on Poliomyelitis. A short time ago Dr. Rosenow entered private practice in Pasadena, Calif.

things which make such evasion necessary to individuals and then compares the technics thus shown by mental patients and to a lesser degree by "normal man" to similar technics shown by the "crowd-man," as he exists in mobs and emotionally motivated movements. He reminds us that it has been pointed out that "in a complicated world, men cannot have an accurate picture of reality and consequently they construct a picture of that world which pleases them and which influences their behavior." Actual conditions surrounding people are not so important and determining as their conception of these conditions. Lippmann has labeled this expurgated edition of reality the "stereotype."

Dr. Strecker outlines certain characteristic stereotypes of individuals. He believes that crowds have similar stereotypes and that they develop a crowd-consciousness which can be traced and studied in the same way as that of a person and which influences the behavior similarly. The unfortunate aspect of the crowd-man as he exists in his group, is that "every spiritual superiority may be lopped off to the common measure and every little ego-consciousness may be stretched to the stature of full manhood. A small mind in a huge body is scarcely helpful in furthering an intelligent facing of reality." The crowd-man has obvious inferiorities, among the chief ones being his mediocre capacities, his commonplaceness and the childish character of his behavior.

This gives some general idea of his feeling about the working and ungoverned violence completely uncontrolled by intelligence, but directed by emotion, which is likely to emerge in propaganda-directed groups. This has led our civilization and our cultures into serious predicaments which merit psychiatric study in order to get some perspective into the motivations of behavior.

The last third of the book represents such a study. "When the psychiatrist looks at crowd-mindedness, whether it be in the emotional debauch of this or that movement or in a violent mob or in a nation at war, he simply sees on a large scale that which often he has observed at close range in his patients." Dr. Strecker believes the solution of the problem lies in individual education, aiming toward making it easier for the individual to recognize reality as it is and in taking some steps toward fixing the focus of our present reality on less extroverted ends, thus making it more tolerable and relieving many of the existing pressures. We could wish that Dr. Strecker would be a little more direct.

The book is readable but somehow we get the impression that there is a point which is missed, which would have made it much more usable. It leaves nothing particularly helpful to the individual in meeting the world as it is, nor does it give him any definite suggestions as to anything he can do toward altering it. This criticism is probably unjust, in that it applies not only to this volume, but to much of the mental hygiene propaganda.

H. M. M.

Dr. William B. Castle, F.A.C.P., Boston, was elected president of the American Society for Clinical Investigation at its recent annual session. Dr. Eugene M. Landis, F.A.C.P., University, Va., is secretary of this Society.

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Dr. D. M. Holt, F.A.C.P., Greensboro, N. C., Chairman of the Public Relations Committee of the North Carolina State Medical Society for the past year, was elected First Vice President of the North Carolina State Medical Society at the last annual meeting of the Society at Pinehurst, N. C. in June. He was also reelected Chairman of the Public Relations Committee.

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Among the guest speakers at the annual meeting of the Pacific Northwest Medical Association in Spokane, Wash., July 10-13, were:

Dr. Andrew B. Stockton (Associate), Assistant Clinical Professor of Medicine, Stanford University School of Medicine, San Francisco;

Dr. Anton J. Carlson, F.A.C.P., Frank P. Hixon Distinguished Service Professor of Physiology, Division of Biological Sciences, University of Chicago;

Dr. Fred H. Kruse, F.A.C.P., Clinical Professor of Medicine, University of California Medical School, San Francisco;

Dr. William Edward Chamberlain, F.A.C.P., Professor of Radiology and Roentgenology, Temple University School of Medicine, Philadelphia;

Dr. Harold E. Robertson, F.A.C.P., Pathologist at the Mayo Clinic, Rochester, Minn.

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Dr. Stuart Pritchard, F.A.C.P., Battle Creek, Mich., recently received the honorary degree of doctor of science from the University of Michigan, Ann Arbor, for "distinguished and outstanding contributions to the field of medicine and public health."

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The speakers at the 73rd annual meeting of the Mississippi State Medical Association, held in Jackson, included the following:

Dr. Douglas D. Baugh, F.A.C.P., Columbus, Miss.—"Intercepting Cancer in the Female Reproductive Organs";

Dr. Robert Lyle Motley, F.A.C.P., Memphis, Tenn.—"Some Points in the Diagnosis and Treatment of Indigestion";

Dr. John G. Archer, F.A.C.P., Greenville, Miss.—"Some Observations of Bundle Branch Block";

Dr. Rudolph H. Kampmeier, F.A.C.P., Nashville, Tenn.—"Benign Tertiary Manifestations of Syphilis Presenting Difficulties in Diagnosis."

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At the 58th annual meeting of the New Mexico Medical Society Dr. Carl Mulky, F.A.C.P., Albuquerque, was named president-elect.

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Dr. Walter Reece Berryhill, F.A.C.P., has been named acting dean of the University of North Carolina School of Medicine, Chapel Hill, following the resignation of Dr. William deB. MacNider, F.A.C.P. Dr. MacNider, who has been dean of the School of Medicine since 1937, resigned to continue his research activities as Kenan professor of pharmacology.

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Dr. Homer E. Prince, F.A.C.P., Houston, was elected president of the Texas Allergy Association at its recent annual meeting.

The Committee on Medicine held an organized meeting at Washington, June 29, 1940, which was attended by:

Dr. Arthur L. Bloomfield, F.A.C.P., San Francisco  
 Dr. James D. Bruce, F.A.C.P., Ann Arbor  
 Dr. Roger I. Lee, F.A.C.P., Boston  
 Dr. Warfield T. Longcope, F.A.C.P., Baltimore  
 Dr. Hugh J. Morgan, F.A.C.P., Nashville  
 Dr. Walter W. Palmer, F.A.C.P., New York  
 Dr. James E. Paullin, F.A.C.P., Atlanta  
 Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia

and Dr. Russell Wilder, F.A.C.P., Rochester, Chairman, members of the Committee; Dr. L. H. Weed, Chairman of the Division of the Medical Sciences; and by invitation, Surgeon General James C. Magee, F.A.C.P., U. S. Army; Brigadier General S. U. Marietta, F.A.C.P., U. S. Army; Colonel C. C. Hillman, F.A.C.P., U. S. Army; Lieutenant Colonel James S. Simmons, F.A.C.P., U. S. Army; Captain L. E. Griffis, U. S. Army; Commander C. S. Stephenson, U. S. Navy; and Commander John R. Poppen, F.A.C.P., U. S. Navy. The meeting was devoted to a discussion of problems in the solution of which this Committee will be called upon for assistance. It was proposed that an executive committee be set up, consisting of chairmen of main committees with representation from the Army, Navy and Public Health Service. To this executive committee may come recommendations from the Committee on Medicine and the other main committees. The following sub-committees were established:

*Infectious Diseases*

Dr. Francis G. Blake, F.A.C.P., *Chairman*  
 Dr. Rollo E. Dyer  
 Dr. Henry Helmholtz  
 Dr. Chester S. Keefer, F.A.C.P.  
 Dr. Stuart Mudd  
 Dr. Thomas M. Rivers

*Venereal Diseases*

Dr. J. Earl Moore, *Chairman*  
 Dr. Edwin P. Alyea  
 Dr. Charles Walter Clarke, F.A.C.P.  
 Dr. Oscar F. Cox, Jr.  
 Dr. J. F. Mahoney  
 Dr. John H. Stokes

*Tropical Medicine*

Dr. W. A. Sawyer, *Chairman*  
 Dr. Mark F. Boyd  
 Dr. Edward H. Hume  
 Dr. Thomas T. Mackie, F.A.C.P.  
 Dr. Henry E. Meleney  
 Dr. Robert B. Watson, F.A.C.P.

*Cardiovascular Diseases*

Dr. Paul D. White, F.A.C.P., *Chairman*  
 (Personnel to be selected)

*Tuberculosis*

Dr. Esmond R. Long, *Chairman*  
 (Personnel to be selected)

*Nutrition*

Dr. Russell M. Wilder, F.A.C.P., *Chairman*  
 Dr. V. P. Sydenstricker, F.A.C.P.  
 Dr. Tom D. Spies, F.A.C.P.

At the recent annual meeting of the American Society for the Study of Allergy, Dr. Robert L. Benson, F.A.C.P., Portland, Ore., took office as president; Dr. Milton B. Cohen, F.A.C.P., Cleveland, Ohio, was chosen president-elect, and Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill., was elected vice president. Dr. James Harvey Black, F.A.C.P., Dallas, Tex., is secretary of this Society.

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Dr. John H. Peck, F.A.C.P., Oakdale, Iowa, was installed as president and Dr. Benjamin Goldberg, F.A.C.P., Chicago, Ill., was named president-elect of the American College of Chest Physicians at their recent annual meeting in New York, N. Y. Dr. J. Winthrop Peabody, F.A.C.P., Washington, D. C., and Dr. Mathew Jay Flipse, F.A.C.P., Miami, Fla., were elected vice-presidents of this society.

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Dr. Alan Brown, F.A.C.P., Toronto, Canada, was recently made a fellow of the Royal College of Physicians of London (*honoris causa*).

## REGIONAL MEETING OF MARYLAND MEMBERS

Fellows and Associates of the American College of Physicians residing in Maryland hold two local meetings each year. The spring meeting was held in connection with a dinner at The Maryland Club, Baltimore, on Saturday, May 18, 1940, with forty-two members present. Dr. Louis Krause, College Governor for Maryland, presided and opened the meeting. Dr. W. Halsey Barker (Associate), Secretary, read the minutes of the preceding meeting. The Maryland group, which they currently call the "Maryland Chapter," regularly elects a chairman and a secretary each year. Dr. Wetherbee Fort, F.A.C.P., was elected president for 1940-41, and Dr. R. Carmichael Tilghman (Associate), secretary. The main purpose of the spring meeting was to report the events of the Cleveland Session of the College. Dr. M. C. Pincoffs, F.A.C.P., opened the discussion by commenting on the papers on military medicine, which he considered opened a new field of medical work. Dr. Sydney R. Miller, F.A.C.P., discussed the requirements for admission to the College, emphasizing that Associates elected in the future shall be required to be certified by one of the national certifying boards before becoming eligible for advancement to Fellowship. The local chapter expressed regret at Dr. Miller's retirement from the Committee on Credentials after many years of valuable service.

Excellent accounts were given of the scientific and social programs of the Cleveland Session by many of the members who had attended the Meeting, chief among whom were Drs. Settle, Legge, Beck, Gundry, Acton, and Tenner. Out of the discussions came suggestions for improvement in clinics, panel discussions, and scientific papers. A suggestion was further made that improved amplifying service be used in the larger clinic rooms. Dr. Pincoffs was asked if it would be feasible to have a reporter record the discussions of the clinics with the object of publishing these in the ANNALS. The Editor stated that this procedure had been tried previously but had not proved satisfactory.

After Dr. Krause read excerpts from the chief banquet address of Mr. Grove Patterson, Editor of the *Toledo Blade*, the meeting adjourned.

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Dr. Louis Faugères Bishop, Jr., F.A.C.P., New York City, was elected President of the American Therapeutic Society for the year 1940-41 at the 41st Annual Meeting of this Society in New York City, June 7-8, 1940.

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At the expiration of his term as Governor of the American College of Chest Physicians for the State of Wisconsin, Dr. Andrew L. Banyai (Associate), Wauwatosa, was elected Regent of that College for District No. 9, at the recent annual meeting of the American College of Chest Physicians held in New York City. Dr. Banyai presented a paper at this meeting on "Newer Aspects of Pneumoperitoneum Treatment of Pulmonary Tuberculosis."

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Before a joint meeting of the sections on Medicine and Gastroenterology of the New Jersey State Medical Society, held in Atlantic City, N. J., June 4, 1940, Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, presented a paper on "The Essentials in Digestion and Absorption in Deficiency Disease." He was also awarded first prize for an exhibit on Deficiency Disease.

Dr. Kelly also presented an exhibit on Deficiency Disease before the Scientific Section of the American Medical Association Convention in New York, N. Y., June 10-14.

Council, and as President of Section V during 1932-33. He was Honorary Adviser in Public Health Administration of the Department of Health, Ontario, and Honorary Consultant of the Victorian Order of Nurses.

We have lost a man of rare gifts and rarer vision at an age at which rich fruits of a ripened judgment might have been the expected harvest for many years to come. The honors won by Dr. FitzGerald have brought unique lustre to Canadian Medicine. The memory of his gentle yet forceful personality will long live among his colleagues here and abroad.

J. HOWARD HOLBROOK, M.D., F.A.C.P.,  
Governor, Province of Ontario

### DR. OTIS BURGESS SPALDING

Lieutenant Commander Otis Burgess Spalding (Fellow, 1931), Medical Corps, United States Navy, was born November 14, 1875, in San Francisco, California, where he received his early education. He attended the University of California during the years 1893 and 1894 and graduated from Leland Stanford Jr. University Medical School (Cooper Medical School) in the class of 1898.

Following graduation, he served as ship's surgeon on the S. S. Maui. The years 1901 and 1902 were spent in postgraduate work in gynecology and obstetrics at Vienna, Berlin, and Dublin. He served as surgeon in the Women's Hospital, San Francisco, California, 1902-1903. From 1903 to 1917 he practiced his specialty of surgery, gynecology and obstetrics in his home city.

In 1917 he enrolled in the naval reserve and served as senior medical officer at the Naval Reserve Training Camp, San Pedro, California, and transferred to the regular service in November 1919. During his service in the Medical Corps of the Navy, he served in the x-ray departments of the Naval Hospital, Mare Island, California; the U. S. S. *Relief*; the Naval Hospital, Washington, D. C., and the Naval Hospital, San Diego, California. He was placed on the retired list of officers of the Navy on December 1, 1939, and died April 12, 1940.

Dr. Spalding was elected to Fellowship in the American College of Physicians in 1931. He was registered with the Council of Medical Education and Hospitals in 1933 as a fully qualified roentgenologist. In 1934 he was elected to Fellowship in the American College of Radiology.

The entire service record of Dr. Spalding is one of which his corps may well be proud. The possessor of a winning personality, sound judgment, and unimpeachable character, his was the type that adds lustre to his profession. The high order of his professional skill was evidenced particularly in his instruction of junior officers. He was exceptionally well informed and efficient as a roentgenologist and was well versed in physical

Dr. Soma Weiss, F.A.C.P., Boston, was one of the faculty of the 24th annual graduate medical course held at the University of Washington, Seattle, July 15-19, 1940.

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Dr. Paul F. Dickens, F.A.C.P., Washington, D. C., spoke on "Diagnosis and Treatment of the Anemias" at the 21st annual session of the Association of Former Interns of Freedmen's Hospital, Washington, D. C.

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Lieutenant Colonel Edgar E. Hume, F.A.C.P., Washington, D. C., recently addressed the Innominate Society, Louisville, Ky., on "The Army Medical Library of Washington and Its Collection of Early Kentuckiana."

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Under the presidency of Dr. Burton R. Corbus, F.A.C.P., Grand Rapids, Mich., the Upper Peninsula Medical Society held its annual meeting in Menominee, July 10-11. Among the speakers on the scientific program of this meeting was Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., who spoke on "Treatment of the Menopause."

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Dr. Thomas K. Lewis, F.A.C.P., Camden, N. J., was named president-elect and Dr. Ralph K. Hollinshed, F.A.C.P., Westville, N. J., was named second vice president of the Medical Society of New Jersey at the annual meeting in Atlantic City, June 4-6, 1940.

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Dr. Hubert B. Haywood, F.A.C.P., Raleigh, N. C., was installed as president of the Medical Society of the State of North Carolina at its recent meeting in Pinehurst.

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Dr. Noble Wiley Jones, F.A.C.P., Portland, Ore., spoken on "The Problem of Atherosclerosis and Atherosclerotic Heart Disease" at the recent annual meeting of the Southern Oregon Medical Society in Ashland.

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Dr. Ernest P. McCullagh, F.A.C.P., Cleveland, conducted a clinic and spoke on "Clinical Values of Testicular Hormones" at the annual spring clinic of the Lycoming County Medical Society held in Williamsport, Pa.

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Dr. Martha Tracy, F.A.C.P., Assistant Director of Public Health of Philadelphia and retiring Dean of the Woman's Medical College of Pennsylvania, was recently honored at a dinner. Dr. Tracy had been Dean of the Woman's Medical College of Pennsylvania since 1918, but, because of her appointment as Assistant Director of Public Health, retired at the end of the college year.

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Dr. Francis D. Murphy, F.A.C.P., Milwaukee, Wis., spoke on "Use of Sulfanilamide and Allied Compounds in Clinical Medicine" at an all-day program of the Marquette University School of Medicine Alumni Association in Milwaukee.

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Dr. Alexander E. Brown, F.A.C.P., Rochester, Minn., addressed a recent meeting of the Medical Society of Milwaukee County (Milwaukee, Wis.) on "Sulfapyridine and New Compounds."



Society, and the American College of Physicians. He was a member of the staff of the Collis P. Huntington Memorial Hospital of Pasadena. He belonged to the Oneonta Club, the Annandale Country and other Southland clubs. He was a member of St. James Episcopal Church of South Pasadena.

Dr. Speik had a large and very active medical practice, and was widely known both in professional and civic circles. His large circle of friends and acquaintances join with his family in their sorrow for the loss of a good physician, husband and father.

EGERTON L. CRISPIN, M.D., F.A.C.P., Regent.

#### DR. ALBERT W. LEWIS, JR.

Dr. Albert W. Lewis, Jr., Atlanta, Ga., thirty-nine years of age, died May 13, 1940, after an illness of several months. Dr. Lewis was a native of Tennessee and graduated from the University of Tennessee College of Medicine in 1932. He was well known and liked in Atlanta where he was on the staffs of Grady Hospital and Piedmont Hospital. He was also Assistant in Medicine and Assistant in Pharmacology at the Emory University School of Medicine. He was a member of the Fulton County Medical Society, Georgia Medical Association, Southern Medical Association and an Associate of the American College of Physicians.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,  
College Governor for Georgia

#### DR. HARRIS HOWARD HAMLIN

Dr. Harris Howard Hamlin (Associate), Seattle, Wash., died suddenly March 19, 1940, of coronary occlusion. Dr. Hamlin had been disabled since a previous coronary attack in February, 1939, this being the second.

Dr. Hamlin was born in Seattle, September 11, 1896. He was graduated with the degree of Bachelor of Arts from Stanford University in 1922 and with the degree of Doctor of Medicine from the University of Kansas School of Medicine in 1929. He served his internship at the Montreal General Hospital, followed by a residency at the Boston City Hospital from 1930 to 1932.

He began practice in Internal Medicine in Seattle in 1932, and became an Associate of the American College of Physicians in 1938. He was a member of the King County Medical Society, Washington State Medical Association, Fellow of the American Medical Association and also was a member of the Seattle Academy of Internal Medicine. He was a member of the Visiting Staff of the King County Hospital from 1932 until his death.

Dr. Hamlin was high in the personal and professional esteem of those who knew him. The profession and the College have suffered a real loss in his premature death.

C. E. WATTS, M.D., F.A.C.P.,  
Governor for Washington

Dr. Milford O. Rouse, F.A.C.P., Dallas, was elected president of the Texas Society of Gastroenterologists and Proctologists at their third annual meeting held recently.

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Dr. Paul Dudley White, F.A.C.P., Boston, delivered the oration on medicine at a joint meeting of the Medical Society of Virginia and the West Virginia State Medical Association, which was held at White Sulphur Springs, July 29-31. Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., spoke on "The Patient Who Is Always Complaining" at this meeting.

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Dr. Oscar G. Costa-Mandry, F.A.C.P., San Juan, P. R., has been made an honorary member of the Society of Physicians and Surgeons of Costa Rica. Dr. Costa-Mandry is now president of the Puerto Rico Medical Association.

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Dr. Cesar Dominguez (Associate), Humacao, P. R., was recently reappointed a member of the Board of Medical Examiners of Puerto Rico.

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At the recent annual meeting of the Arizona State Medical Association, Dr. William Paul Holbrook, F.A.C.P., Tucson, was chosen president-elect. Dr. Leslie R. Kober (Associate), Phoenix, is vice president and Dr. William Warner Watkins, F.A.C.P., Phoenix, is secretary of this association.

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Dr. Francis Marion Pottenger, F.A.C.P., Monrovia, Calif., has been appointed a member of the state board of health.

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Dr. Robert Lomax Wells, F.A.C.P., was recently elected one of the vice presidents of the Medical Society of the District of Columbia.

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In May Dr. James B. Herrick, M.A.C.P., Chicago, was presented with the "Gold Headed Cane" by the University of California Medical School (San Francisco). Dr. Herrick received this award for his accomplishments in the practice of medicine, in teaching, and in investigation. In June he was awarded the honorary degree of doctor of science at the convocation of Northwestern University.

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New York University College of Medicine, on June 5, awarded the honorary degree of doctor of public health to Dr. Nathan B. Van Etten, F.A.C.P., New York, N. Y.

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Dr. Henry K. Mohler, F.A.C.P., Philadelphia, recently received an honorary degree from Juniata College (Huntingdon, Pa.).

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The Medical Fellowship Board of the National Research Council, Washington, D. C., recently renewed the fellowship in medical science for study in the United States, during the year 1940-41, of Dr. Abe Ravin (Associate), Denver, Colo. Dr. Ravin will continue his study at Harvard University.

any possible effort might be made to spare any deserving member. Governor Walter B. Martin, of Virginia, interceded for Dr. William A. Shepherd (Fellow), Richmond, who he reported had been ill and out of practice. Governor Martin was advised by Chairman Cocke to report the situation to Dr. James E. Paullin, Chairman of the Committee on Public Relations, with the recommendation that dues be remitted because of illness and retirement from practice.

Chairman Cocke made a summary report to the Board of Governors concerning happenings and activities in the College during the past year, including losses by death, new elections, two Masterships, plans for the publication of a College History, additions to the Life Membership Roster and attendance in and success of the 1940 Postgraduate Courses.

At this point, Chairman Cocke called upon Dr. Henry M. Thomas, Jr., Chairman of the Governors' Committee to Survey Postgraduate Courses, to make his report.

DR. HENRY M. THOMAS, JR.: "Mr. President and members of the Board of Governors: This is a rather difficult report to summarize, because it covers a great deal of work, accompanied by sending out questionnaires not only to those pursuing the Courses, but to individual members of the Board of Governors; including also reports obtained from each Governor from those in his territory who pursued the College Courses. A few things came out clearly from the reports. Every one who has taken the Courses is thoroughly enthusiastic about them and delighted that he took the Course and hopes to take more. For instance, one of our members is just back from the Postgraduate Course he took in Iowa City. This is the third year he has taken these Courses and he states they are getting better every year. It would be amiss to go into a long report to tell you of the minor differences which came out of all the reports we assembled. These differences had to do with the time of year for the Courses. We obtained no vote which would allow us to settle that question. We also had no sufficient preponderance of opinion that helped us settle the question of the length of the Courses. One member had asked that there be three kinds of courses given each year—one of one week's duration, one of ten days and one of two weeks, so that men may choose according to the amount of time available from their work. Other points in which there was some difference of opinion concerned whether we should have specific courses or general courses, and where they should be held. In general, it was the clear opinion that these courses should be available, if possible, to the members who are going to the meetings, that they should not be on a date that would interfere with the meetings, many wanted them just before or just after the meetings, whereas some wanted them in the autumn or at some other time. One man suggested that, like the clinics that are given in Vienna by the American Medical Association, there be a bulletin service put in the 'Annals of Internal Medicine' whereby courses might be available pretty much all year long and accredited teachers of the College be allowed to give a course any time they desired, and to have it announced to the members through the journal. The suggestions we obtained were very numerous. We took this matter up as a fact finding committee, rather than a committee to elaborate suggestions, and we turned our findings to the Regents' Committee on Postgraduate Education, of which Dr. Hugh J. Morgan is Chairman.

"I am glad we made this investigation, because I, for one, held a rather narrow-minded conception of the problem. It now is clear to me that this activity of the College is a much more important one than merely pulling ourselves up by our own boot straps, that this program has more to do than just with our own education, that it is a part of the College's activities in the large field of Postgraduate Education. It has been a magnificent success. If one were to try to criticize, the only possible way would be to say that the numbers who have availed themselves of these courses are something in the range of 7 per cent of the members of the College. There are, how-

## OBITUARIES

## DR. JOHN GERALD FITZGERALD

Dr. John Gerald FitzGerald, F.A.C.P., Toronto, Canada, died June 20, 1940, at the age of fifty-seven.

Dr. FitzGerald received his M.B. degree in 1903 and his M.D. degree in 1920 from the University of Toronto Faculty of Medicine. In 1925 he received an honorary degree of LL.D. from Queen's University Faculty of Medicine. He undertook postgraduate study at Harvard Medical School, University of California Medical School and University of Toronto Faculty of Medicine. During the summer of 1910 he studied at the Pasteur Institute of Paris and Brussels, and during the summer of 1911 he studied pathology at Freiburg, Germany. In 1913 he was appointed Associate Professor of Hygiene at the University of Toronto Faculty of Medicine and conceived his plan for a school of hygiene in whose laboratories specific sera and vaccines of high quality and low price could be manufactured, which would serve Canada as a whole and make the school a national center for postgraduate work in public health.

During the World War he served as Major in command of a mobile laboratory in France and later became Assistant Adviser in Pathology to the 5th British Expeditionary Force.

In 1919 Dr. FitzGerald succeeded the late Dr. John Amyot as Professor of Hygiene. He was appointed Director of the Connaught Laboratories, which had been opened in 1917 following the generous gift of the late Sir Albert Gooderham. In 1923 he became a member of the National Health Division of the Rockefeller Foundation, which had provided a building and an endowment for the new School of Hygiene, fulfilling the foresighted ideas of the young scientist in 1913. During 1927 Dr. FitzGerald represented Canada at the Rabies Conference in Paris. In 1930 he was appointed to the Health Division of the League of Nations, on which he served six years and of which he was Vice President during 1933. In 1931 he was made Scientific Director of the National Health Division of the Rockefeller Foundation, and in 1932 he was appointed Dean of the University of Toronto Faculty of Medicine, holding this office for four years. In 1935 he was appointed a member of the Permanent Commission on Biological Standardization of the Health Organization of the League of Nations. In 1938 he became a member of a Subcommittee on Medical Research in the National Research Council of Canada.

Dr. FitzGerald was a Fellow of the Toronto Academy of Medicine, the Royal College of Physicians and Surgeons of Canada, the Canadian Public Health Association, the American Public Health Association, and the American College of Physicians since 1925. He was a member of the Canadian Medical Association, serving on the Executive Committee for many years, and a Fellow of the Royal Society of Canada, serving as a member of the

Chairman Cocke opened the meeting for a discussion of Dr. Thomas' or Dr. Smith's report.

Dr. James J. Waring, Governor for Colorado, said that he had been among those who took the Course in "General Medicine" at the University of Michigan, and the group had authorized him to express unanimously for them their great appreciation of the Course which had been managed and designed by Dr. Cyrus C. Sturgis. The faculty of the Medical Department of the University of Michigan had really spared no effort in any way in giving to the registrants all the information on the side of medical science, as well as every attention socially.

Dr. C. W. Dowden, Governor for Kentucky, reported that he had received many inquiries from non-members of the College about admission to these courses. He inquired if it would not be necessary to limit the attendance to members of the College only. Dr. Dowden recommended that admission to the courses be restricted wholly to members of the College until it became evident that some vacancies would be available, which could be assigned to non-members, especially those preparing for membership in the College or for certification by the American Board.

Secretary Loveland explained that the registration is handled through the Executive Offices of the College. A formal registration form is required, and a matriculation card is issued to each registrant upon payment of the specified fees. Registration for the current courses had been restricted to members, with the exception of the course "Medicine in Industry," for which there was not adequate demand from members, with the result that non-members were admitted.

On motion by Dr. Oliver C. Melson, Governor for Arkansas, seconded by Dr. Fred M. Smith, Governor for Iowa, and carried, Dr. Thomas' report was accepted and filed.

Chairman Cocke reported upon the proceedings of the Board of Regents at its meeting on the previous day.

Dr. Turner Z. Cason, Governor for Florida, reported that there would be a regional meeting of the Florida members of the College in Tampa on April 29, and that a number of doctors from Cuba would be entertained. From this group, the College might appropriately wish to start a College membership in Cuba. Dr. Cason extended an invitation to the Executive Secretary, Mr. Loveland, and to the President-Elect, Dr. James D. Bruce, and to the Chairman of the Board of Governors, Dr. Cocke, to attend. The invitation was extended also to all members of the Board of Governors if opportunity to attend presented itself.

Adjournment.

Attest: E. R. LOVELAND  
*Executive Secretary*

CLEVELAND, OHIO

APRIL 3, 1940

The second meeting of the Board of Governors, in connection with the Twenty-fourth Annual Session, was held April 3, 1940, at the Cleveland Public Auditorium, Cleveland, Ohio, 12:30 o'clock, with Dr. Charles H. Cocke, Chairman, presiding, and Mr. E. R. Loveland acting as Secretary.

The following Governors, or their Alternates, were present: Dr. Fred W. Wilkerson, Dr. Fred G. Holmes, Dr. Lewis B. Flinn, Dr. Turner Z. Cason, Dr. Glenville Giddings, Dr. C. W. Dowden, Dr. Eugene H. Drake, Dr. Henry M. Thomas, Jr., Dr. Robert O. Brown (representing Dr. LeRoy S. Peters), Dr. Charles F. Tenney, Dr. A. B. Brower, Dr. Ernest L. Boylen (representing Dr. T. Homer Coffen), Dr.

therapy. His work in deep therapy and his investigations of psittacosis and silicosis were of a high order.

ROSS T. MCINTIRE, M.D., F.A.C.P.,  
Governor for U. S. Navy

### DR. JOHN W. MOORE

Dr. John William Moore, prominent Charleston physician and Fellow of the College, died following a brief illness on July 20, 1940. He was 70 years of age.

Dr. Moore suffered a heart attack at his office on July 17 and died three days later. He was born at Lexington, Virginia, on November 6, 1869. He received his academic schooling at Washington and Lee University and was graduated in medicine from the University and Bellevue Hospital Medical College, New York City, in 1899. He practiced in Charleston from 1903 to 1917, and then served as a Captain in the Army Medical Corps during the World War. He later spent three years in China as a medical missionary. He then returned to Charleston in 1926 and engaged in private practice until his death.

Dr. Moore was an active business man in Kanawha County. At one time he was superintendent of the Charleston General Hospital, and was serving as superintendent of the Mountain State Hospital at the time of his death.

Dr. Moore married Miss Daisy Preston, of Lexington, Virginia, in 1908. She died in 1921. He later married Miss Laura Dyer Venable, who with one son, John Venable Moore, survives him.

ALBERT H. HOGUE, M.D., F.A.C.P.,  
Governor for West Virginia

### DR. FREDERICK A. SPEIK

Dr. Frederick A. Speik, Fellow (1922), died in South Pasadena June 30, 1940. Dr. Speik was born in Stockton, California, in 1882. He was educated at the University of Chicago where he won all-American football honors in 1904 under the training of his friend, Amos Alonzo Stagg. His medical training was at Rush Medical College where he was graduated with a very high standing. He went to Cook County Hospital for his general medical service.

Dr. Speik began practice in Los Angeles in 1912. He held a professorship in clinical medicine and in the College of Physicians and Surgeons, then the Medical Department of the University of Southern California, and was one of the chiefs-of-staff of the Los Angeles General Hospital. During the war he was an official draft examiner. He was the author of numerous medical papers, and was a member of many professional and social organizations, among which were the Los Angeles County, California State and American Medical Associations, the Los Angeles Clinical and Pathologic

work of the pre-meeting courses where it can best be done and in the hands of those who are most interested.

"I may say that the work of arranging those pre-meeting courses is far greater than one would at first think. One has to select the topics, the place, the man, the man has to be persuaded, and the thing has to be organized. A great deal of that is carried on by your Executive Secretary, and the Executive Secretary in combination with the Chairman of the new committee will, I suppose, as usual, carry the brunt of it, although the Governors of the States in which the pre-meeting courses may be planned ought to coöperate to the fullest. That, as I understand, is the setup, and if Dr. Cocke and Dr. Bruce see faults in that statement or omissions, they can supplement it.

"Now, if I may speak briefly on one other subject, I have no criticism of the duties of the President throughout the year. They are a pleasure. However, if they continue to develop sectional meetings, as the American College of Surgeons has, we are going to run into a problem. As Dr. Bortz will tell you, Dr. George Muller, President of the American College of Surgeons, this last year found that his Presidency turned out to be pretty nearly a full-time job. In that College they have a permanent Chairman of the Board, who takes all the administrative work off the President, carries on with a continuance of knowledge and policy as Dr. Crile did for years, and now Dr. Irving Abel has replaced him. We have no such Chairman of the Board. I am not sure that I favor one, but unless the President is relieved of the program arranging and certainly the administrative duties, he can't take on as much of the sectional meetings as the President of the American College of Surgeons has.

"Now, maybe we ought not to have as many sectional meetings. Maybe we ought to have just as many and that ought to be the President's main job. He would be able to do it if that were his job. I am just presenting the problem, not prejudging it.

"I am very critical of the President's duties at the meeting. He talks a great deal too much. He has to under our present setup. I think it is very unfortunate.

"On the other hand, the Vice Presidents have no duties whatsoever. I would like to work out some scheme whereby the Vice Presidents would be brought more into the picture of the College. Possibly some of the Vice Presidents might be made use of in the sectional meetings as the official representatives of the College. They are fine men. They wouldn't be Vice Presidents if they were not. I think that some of the sectional meetings ought to invite the Vice Presidents, not every one of them the President.

"Second, I think somehow or other the Vice Presidents ought to do some of the talking and relieve the President. He has to make his speech of response on Monday. He has to preside at two meetings of the Board of Regents. He has to speak once or twice at the business meeting, at which he presides. He has to speak at the Banquet. He has to deliver a Presidential Address. I think there are seven speeches; I have forgotten two or three of them. Then, gentlemen, he is invited to a very delightful lunch and asked to speak again.

"Cancer of the larynx in our Presidents, Dr. Bruce, shows a very high incidence from chronic irritation, and I think that it is not only hard on him, but it is hard on the membership. I think they would much rather hear three less speeches from him and one more from each of the Vice Presidents. Thank you." (Applause.)

Chairman Cocke then introduced President-Elect James D. Bruce.

DR. BRUCE: "Mr. Chairman, Mr. President and gentlemen: There is nothing I can add to what Dr. Pepper has said. The delegation of more duties in Postgraduate Education to the Board of Governors I heartily approve, the utilization of all the

# MINUTES OF THE BOARD OF GOVERNORS

CLEVELAND, OHIO

APRIL 1, 1940

The first meeting of the Board of Governors, held in connection with the Twenty-fourth Annual Session of the American College of Physicians, occurred on April 1, 1940, at the Cleveland Public Auditorium, Cleveland, Ohio, 5:10 p.m., with Dr. Charles H. Cocke, Chairman of the Board, presiding, and Mr. E. R. Loveland, Executive Secretary, acting as Secretary of the meeting.

The following Governors, or their Alternates, were present: Dr. Fred W. Wilkerson, Dr. Fred G. Holmes, Dr. Lewis B. Flinn, Dr. Turner Z. Cason, Dr. Glenville Giddings, Dr. James G. Carr, Dr. C. W. Dowden, Dr. Eugene H. Drake, Dr. Henry M. Thomas, Jr., Dr. Robert O. Brown (representing Dr. LeRoy S. Peters), Dr. Charles F. Tenney, Dr. A. B. Brower, Dr. Ernest L. Boylen (representing Dr. T. Homer Coffen), Dr. M. D. Levy, Dr. Ramon M. Suarez, Dr. James F. Churchill, Dr. James J. Waring, Dr. Charles H. Turkington, Dr. Wallace M. Yater, Dr. Samuel E. Munson, Dr. Robert M. Moore, Dr. Thomas Tallman Holt, Dr. William B. Breed, Dr. Warren Thompson, Dr. Nelson G. Russell, Sr., Dr. Leander A. Riely, Dr. Edward L. Bortz, Dr. R. R. Snowden, Dr. John L. Calene, Dr. J. Owsley Manier, Dr. G. Gill Richards (representing Dr. Louis E. Viko), Dr. Harry L. Arnold, Dr. J. Howard Holbrook, Dr. Oliver C. Melson, Dr. Ernest H. Falconer, Dr. Fred M. Smith, Dr. Joseph E. Knighton, Dr. Henry R. Carstens, Dr. Edgar van Nuys Allen, Dr. Charles H. Cocke, Dr. Alexander M. Burgess, Dr. Kenneth M. Lynch, Dr. Paul K. French, Dr. Walter B. Martin, Dr. Charles E. Watts, Dr. Albert H. Hoge, Dr. Robert D. Roach (representing Dr. Hugh A. Farris), Dr. Charles F. Moffatt, Comdr. Eben E. Smith (representing Rear Admiral Ross T. McIntire) and Dr. Thomas Parran.

The Secretary read abstracted Minutes of the preceding meetings of the Board of Governors, which were approved as read.

Chairman Cocke addressed the Board briefly, expressing his gratification with the large attendance and welcoming the Alternates to the meeting. He reported a communication from Governor G. W. F. Rembert, of Mississippi, expressing regrets at his inability to attend.

Chairman Cocke requested the Executive Secretary to read a telegram from Dr. Frank J. Sladen, Director of the Postgraduate Course, "Industry in Medicine," just completed at the Henry Ford Hospital, Detroit. Mr. Loveland read the telegram, and Chairman Cocke requested Governor Henry R. Carstens, of Michigan, to bear to Dr. Sladen, on behalf of the Board of Governors, its commendation for his excellent work in directing this Postgraduate Course.

Secretary Loveland distributed lists of candidates for Fellowship and Associateship who had been elected by the Board of Regents, so that each Governor would be informed from the beginning of the meeting as to new members elected from his territory. The list is not hereunder repeated, because it appears in the Minutes of the Board of Regents of March 31, 1940.

At the request of the Chairman, Mr. Loveland then distributed a list of the Associates who had been dropped for failure to qualify for Fellowship within the maximum five-year period, as prescribed by the By-Laws. Members of the Board were given an opportunity to ask questions about any particular cases.

At the request of the Chairman, Mr. Loveland also presented the list of members who were subject to being dropped for delinquency in dues of two or more years' standing. Each Governor had previously been advised of each delinquency, so that



tion from Kansas City. Dr. Griffith made a point of the fact that Kansas City had been inviting the College for years, and extended a whole-hearted welcome to the organization.

At this point, Dr. William B. Breed moved that the Board of Governors recommend to the Board of Regents that the College select Boston. The motion was seconded by Dr. Charles F. Tenney, Governor for Eastern New York, put to a vote and carried.

After the reading of some general announcements, the meeting adjourned.

Attest: E. R. LOVELAND,  
*Executive Secretary*



ever, four or five times that number who ask about the courses each year and who may take courses in future years, when courses suit their particular needs and when conditions make it possible for them to attend.

"Our plan of investigation included a letter to every Governor, asking him to send a report from every man in his territory who had taken the Courses. Here again our report is limited to the men who have taken the courses and not to the 93 per cent of the members who have not taken the courses, so that our report does not express an opinion of the College, but merely an opinion of those members who have taken the courses. There were many helpful suggestions as to methods of giving these courses. Some letters were quite critical and some of them were amusing, but most of them were entirely commendatory.

"I, as Chairman of this Committee, had some experience in giving one of the Courses for the College at Johns Hopkins. To give a course of two weeks, or two courses as we did, is an undertaking which requires a great deal of effort on the part of the faculty. It was very strong in my mind that the College was asking Johns Hopkins, the University of Maryland, the University of Pennsylvania, Harvard University and other institutions to do this Postgraduate Education for them, and so I approached the problem with a different slant. I may say that not a single member of our Committee, besides myself, joined in this opinion, so that when I asked them about this phase of it, they all were enthusiastic about continuing the courses along the lines we had already started. I was not interested in changing the method, but I did wonder whether inside our College we couldn't do more about it, and if when we go to Baltimore we couldn't have our College members do the job, or do most of the difficult work, and whether we could not send important Officers of the College to consult with the heads of departments. That suggestion was forwarded to Dr. Morgan's Committee, as were also all of our reports and the letters from each member of our Committee.

"I have tried to give you a resumé of our work and of the type of information that came from it, and report the fact that we made no immediate suggestions, except to pass on our facts to the Regents' Committee. We were informed by Dr. Hugh J. Morgan that our survey had been very helpful, and that a good many of the things had been incorporated in this year's plans."

Dr. Fred M. Smith, Governor for Iowa, who had just completed the direction of one of the College Postgraduate Courses in Cardiology, was asked for a report by Chairman Cocke.

DR. SMITH: "Dr. Cocke and gentlemen: In our Postgraduate Course at Iowa City we had a very fine group of men, and it was with considerable regret we saw them leave. The success of a course of this sort depends on someone being on the job all the time to see that everything is carried out. Not only that, but I have a feeling that any success that we may have had was dependent to a large extent on the fact that these conferences were made very informal. We really tried to get acquainted with these doctors. We began our work in the morning, and followed that with a clinic. Dr. Edgar V. Allen, College Governor for Minnesota, was with us one day and we had him give a clinic that day. Immediately after luncheon there was a period for round table discussion. These men were very free in asking questions. This was encouraged by the informality of the luncheons. The round table discussions were particularly helpful, an opinion in which Dr. Allen readily concurred. They gave each man an opportunity to discuss questions that certainly weren't brought out in the clinic, or, for that matter, in the morning's proceedings. We felt very happy about their attitude, and we felt that they really honored us in coming, and these doctors came all the way from Oregon, California, Louisiana, Pennsylvania and other States."

conflicting reports.<sup>4, 13, 14, etc.</sup> Lerner,<sup>15</sup> although noting symptomatic improvement and at times striking relief of edema, was unable to find significant blood pressure or pulse rate changes. Frommel<sup>10</sup> noted a decreased heart rate in frogs, but an increase in guinea pigs and rabbits. The observations of Schube<sup>14</sup> (who used Coramine to control the narcosis produced by barbiturates), probably represents the predominant opinion in the literature when he states: "the pulse rate and volume in no individual were altered appreciably by Coramine. Likewise the blood pressure was not altered appreciably, regardless of whether arteriosclerosis was present or absent, and irrespective of the presence of normal, low or high pressure." It is probable, as Henderson states,<sup>3</sup> that "blood pressure may rise as a secondary consequence of improved respirations and partly due to the general stimulant effect on the reflex centers, of which the vasomotor center is one."

Mention is occasionally made of diuresis following treatment with Coramine, but this factor has not been stressed either in a positive or negative manner. We have not been able to find records of vital capacity or of blood circulation time in cases with cardiac disease receiving Coramine, nor have we noted studies of intrathecal pressure changes. Schlösser and Schwarz,<sup>32</sup> as a result of the use of Cardiazol and Coramine, noted a significant lowering of venous pressure, in most of their cases with cardiac failure, simultaneous with subjective improvement.

Our purpose has been to observe the effects of Coramine on patients with cardiac disease investigating particularly its action in cases with respiratory distress. Four groups of patients were selected for these studies: *Group 1*: The effect on severe respiratory distress. *Group 2*: The effect on certain signs which might reflect cardiac efficiency. *Group 3*: The effect on intrathecal pressure. *Group 4*: The effect on venous pressure.

#### EFFECT ON RESPIRATORY DISTRESS

A group of patients have been selected who presented themselves with evident respiratory embarrassment, and in whom it was felt that response could be measured by disappearance of Cheyne-Stokes respirations, or a lessening in the number and severity of attacks of paroxysmal dyspnea. *Thirteen* trials were conducted on *ten* patients. The case histories are presented in this report, and table 1 summarizes the results. In most instances Coramine was administered by mouth in doses of 3 to 5 c.c., and repeated four or five times daily, although in two cases (2 and 4) it was given intramuscularly, and in one case (7) oral administration was preceded by a single intravenous injection. The response in cases 3 and 26 was insignificant, and case 5 on one trial (Nov. 1938) failed to derive any relief. In seven instances which responded to Coramine, an attempt was made to control the response by temporary withdrawal of the medication. Upon withdrawal of Coramine from these cases (1, 2, 4, 5 (March 1939), 7, 8, 25) six

M. D. Levy, Dr. Ramon M. Suarez, Dr. James F. Churchill, Dr. James J. Waring, Dr. Charles H. Turkington, Dr. Wallace M. Yater, Dr. Samuel E. Munson, Dr. Robert M. Moore, Dr. Thomas Tallman Holt, Dr. William B. Breed, Dr. Warren Thompson, Dr. Nelson G. Russell, Sr., Dr. Edward L. Bortz, Dr. John L. Calene, Dr. J. Owsley Manier, Dr. G. Gill Richards (representing Dr. Louis E. Viko), Dr. J. Howard Holbrook, Dr. Oliver C. Melson, Dr. Ernest H. Falconer, Dr. Fred M. Smith, Dr. Joseph E. Knighton, Dr. Henry R. Carstens, Dr. Edgar van Nuys Allen, Dr. A. Comingo Griffith, Dr. Charles H. Cocke, Dr. Leonard H. Fredricks (representing Dr. Julius O. Arnson), Dr. Alexander M. Burgess, Dr. Orlando B. Mayer (representing Dr. Kenneth M. Lynch), Dr. Walter B. Martin, Dr. Charles E. Watts, Dr. Albert H. Hoge, Dr. Robert D. Roach (representing Dr. Hugh A. Farris), Dr. Charles F. Moffatt and Comdr. Eben E. Smith (representing Rear Admiral Ross T. McIntire). President O. H. Perry Pepper and President-Elect James D. Bruce attended as guests.

Secretary Loveland gave a brief review of the Minutes of the preceding meeting, and offered to read the full transcript, which, however, was not called for.

Chairman Cocke introduced President Pepper, who addressed the Board as follows:

"The duties of the Committee on Postgraduate Education have grown enormously, just as the College's participation in postgraduate education has grown enormously. The duties of the Committee on Postgraduate Education seem to divide themselves pretty clearly into two parts. There was that part which had to do with the policy of the College, and that involved the representation on the Conference Committee, which combines, as you know, the Council on Medical Education and the American Board, which in itself is going to be no small task because that Committee is eventually going to have the duty of passing on the qualifications of hospitals as reported to them by their field investigators. Secondly, that Committee had all matters of policy brought up to it, and those might be considerable in any year and might not.

"Then on the other half of the main division were the details of the matters with regard to the pre-meeting courses, an activity of the College that has proved very valuable, not only to the members who have taken the course but to many of the gentlemen who have given the courses, who have admitted that they think they have learned more from them and their hospitals were more stimulated by them than even the men who attended them.

"Now, it seemed to me that it was impossible to ask one man to carry that load, as Dr. Hugh J. Morgan has done in the past year or so, and in searching for a solution, it seemed there was a very logical one, and that was to keep the policy in the hands of the same committee, if Dr. Morgan could be persuaded to continue, to keep those matters in the hands of the Regents, who have the power to expend funds, but to create a new committee which would interest itself in developing the pre-meeting courses to an even higher level than they at present are, and to correlate perhaps those pre-meeting courses in some way—this is still all undecided—with sectional meetings perhaps, or even develop new programs along that line.

"Now there we approached a part of this general matter which comes much closer to the Board of Governors and the individual Governors than it does to the smaller body of Regents, and so I ventured to suggest that the work of that committee be subdivided into two committees, one of them remaining a committee largely or altogether of Regents, although that is not necessary; the second committee largely but perhaps not necessarily (this is in the hands of Dr. Bruce, of course) a committee of Governors. That has struck a responsive note in the thoughts of the Regents, and this new committee was authorized at the meeting of the Board of Regents. It seems to me that it offers a solution of the difficulties of the situation and puts the

TABLE I—Continued

Case Number	Diagnosis	Type of Distress	Dosage	Results	Effect of Withdrawal	Again Started Coramine	Effect
5	Art. scl. hypertension; CE; premature beats; MI; Class IV	Feb. 1939 Cheyne-Stokes severe dyspnea. (O.P.D.)	4 c.c. p.o. 4 i.d. 3 wks.	Cheyne-Stokes relieved in 24 hrs. Dyspnea gone in 2 wks. Worse after 3 wks. with failure and dig. toxic			
		March 1939 Cheyne-Stokes	4 c.c. p.o. 5 i.d. 4 days	Regular breathing within 24 hrs.	Reverted to Cheyne-Stokes in 3 days		
6	Art. scl. hypertension; CE; NSR; MI; Class IV	Cheyne-Stokes 3 attacks in 6 mo.	2 c.c. p.o. 4 i.d.	Cheyne-Stokes controlled in 24-48 hrs.			
7	Art. scl. hypertension; CE; gallop rhythm; Class IV	Cheyne-Stokes (Cardiac psychosis)	5 c.c. i.v. then 3 c.c. p.o. q 3 h 5 days	On 2d day normal breathing followed Coramine for 1½-2 hrs. From 3-5 days normal	Reverted to Cheyne-Stokes in 2 days	3 c.c. p.o. q 3 h.	Normal after 24 hours of this drug
8	Art. scl. hypertension; CE; NSR; MI; Class IV	Paroxysmal dyspnea	4 c.c. p.o. 5 i.d. 4 days	Decreased number and severity of attacks. None after 2d day (Nausea)	Severe paroxysmal attacks in 2 days	3 c.c. p.o. 5 i.d.	No attacks after 12 hrs. Temporary withdrawal on 13th day and had attacks next day
25	Art. scl. hypertension; CE; NSR; MI; Class IV. Recent hemiplegia	Cheyne-Stokes	4 c.c. p.o. 5 i.d. 5 doses	Normal breathing, within 24 hrs.	Reverted to Cheyne-Stokes in 8 hrs.	4 c.c. p.o. 5 i.d. 1 day then 3 c.c. p.o. 5 i.d. 10 days	Normal respirations except for hiccoughs and temporary nausea
26	Art. scl.; CE; occasional P.B.; MI; Class IV	Cheyne-Stokes	4 c.c. p.o. 5 i.d. 7 days	No relief			

Officers of the College, related particularly to the Vice Presidents—there again I find a responsive cord. . . .

"I assure you you will find me collaborating very effectively and very heartily in the matters the President has introduced."

Chairman Cocke recognized at this point Dr. Alexander M. Burgess, Governor for Rhode Island.

DR. BURGESS: "I have a particular case to present. A man among my associates, who is one of the best qualified men, told me recently that he had just qualified for the American Board of Internal Medicine, and that he thought therefore it would not be worth his while to seek Fellowship in the American College of Physicians. He said that he felt certification by the Board was all he wanted, or needed, in his community, and that Fellowship in the College would cost a great deal too much."

Dr. Burgess said that this young man was sacrificing his time for his clinics, is not getting along very fast financially and finds the matter of qualifying for certification and Fellowship in the College beyond his convenient reach. Dr. Burgess expressed the fear that this same attitude might be taken by many good men and inquired whether any consideration would be given to the further reduction of fees.

Chairman Cocke asked for discussion of the question, and reported that he had not observed this situation in his part of the country, which is less densely populated, with fewer medical centers and where men do not have the same opportunities which encourage them to seek those opportunities and advantages which the College affords.

Dr. G. Gill Richards, as a representative of the American Board of Internal Medicine, announced that it is contemplated, within the rather near future, that fees for the examination may be somewhat reduced. The reduction cannot be made at the present time, because the Board is attempting an affiliation with sub-specialties, to be started next year, and the Board may have to charge a small additional fee to those men who take not only the regular examination for Internal Medicine, but who take a special examination in a sub-specialty. It may be necessary to charge an additional \$10.00 fee to those men. Until the Board can find out just how many are coming up for sub-specialty examination and what expenses that will entail, no definite step can be taken. Dr. Richards further said that he thought it desirable to consider whether or not both the College and the American Board could not together reduce their fees.

Chairman Cocke assured the group that the whole subject was under consideration.

Chairman Cocke called upon the Secretary to present or announce invitations for the 1941 Session of the College, in order that a consensus of opinion might be obtained from the Board of Governors. It was revealed that formal invitations had come from Boston, Baltimore, Philadelphia, Kansas City, Chicago, San Francisco and other cities.

Dr. Cocke asked the representatives from these cities, if present, to make such remarks as they desire.

Dr. William B. Breed, Governor for Massachusetts, was first to extend an invitation to the College to consider Boston, the invitation being extended by the medical schools, the Governor of the State, the Mayor of the City, the Chamber of Commerce, the medical societies and other groups.

Dr. Henry M. Thomas, Jr., Governor for Maryland, on behalf of Baltimore, stated that he felt it was very near Baltimore's turn for another Session of the College and that the Baltimore members are very anxious to extend an invitation and welcome the College there.

Dr. Edward L. Bortz, Governor for Eastern Pennsylvania, spoke on behalf of Philadelphia and presented the written invitations from the medical schools, the Philadelphia County Medical Society, the Chamber of Commerce, and other agencies.

Dr. A. Comingo Griffith, Governor for Missouri, spoke on behalf of the invita-

TABLE II  
Effect of Coramine \* on Circulatory Signs

Case	Diagnosis	Duration of Coramine Treatment	Art. Blood Pressure	B.C.T.	Pulse	V.C.	Diuresis	E.K.G.
5	Art. Scl.	14 days	Wide variations	39sec. (31)	90 (100)	1000 c.c. (1400)	None	PR 0.24, QRS 0.12 Marked T changes (No change)
9	Art. Scl.	10 days	110/80 (110/80)	35sec. (39)	76 (78)	1200 c.c. (1800)	None	Left B.B.B. (No change)
10	Luetic AI	12 days	155/55 (150/50)	30sec. (25)	80 (80)	1400 c.c. (1200)	None	PR 0.22, QRS 1 and 2 low amplitude (PR 0.2, QRS 1 and 2 normal)
11	Rh.MS, MI	11 days	140/78 (140/76)	38sec. (28)	80 (80)	1700 c.c. (1800)	None	Marked T changes (No change)
12	Art. Scl.	10 days	115/75 (110/72)	25sec. (26)	90 (90)	1800 c.c. (1700)	None	Severe myocardial damage (No significant change)
13	Art. Scl.	9 days	180/110 (210/100)	26sec. (40)	85 (90)	800 c.c. (1500)	Lost 7 lbs.	Marked T changes (No change)

\* Dosage in each case was 3 c.c. p.o. 4 i.d.

(—) Indicates readings at end of treatment.

B.C.T. Blood circulation time (saccharin arm to tongue).

V.C. Vital capacity.

These cases receiving Coramine showed no significant change in blood pressure; the apparent changes in case 13 represent a fluctuation noted frequently in this patient during his hospitalization. The blood circulation time improved in three cases, was uninfluenced in one case, and became prolonged in two cases. Pulse rates were fairly constant, case 5 showing a slight increase. Although the vital capacity increased moderately in three cases there was little change in the others. Only one case showed evidence of weight loss. Electrocardiographic patterns remained nearly unchanged.

recorded until it showed no tendency to vary for at least 10 minutes. Accepting this as a basal level, 5 c.c. of Coramine were given intravenously over a period of 3 to 4 minutes and readings of the pressure recorded at short time intervals. Given in this manner, and the dose is admittedly large, Coramine caused most patients to complain within two or three minutes of the onset of the administration, of a sensation of burning heat over the body, followed by perspiration and restlessness. Burning and itching of the face, especially of the nose, were occasionally encountered. This picture in one patient (case 5) was attended with considerable excitement, and it is felt that these symptoms are due to widespread cerebral stimulation. No nausea nor palpitation was noted. In all cases there has been a resultant drop in intrathecal pressure, the maximum being reached in from 10 to 20 minutes. (Table 3.)

Four patients in this group (cases 16 and 5 (figures 1 and 2) and cases 17 and 24) showed an initial rise of intrathecal pressure, associated with

# ANNALS OF INTERNAL MEDICINE

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## OBSERVATIONS UPON THE EFFECT OF CORAMINE IN CERTAIN CARDIAC STATES\*

By WILLIAM D. STROUD, M.D., F.A.C.P., and PAUL H. TWADDLE, M.D.,  
*Philadelphia, Pennsylvania*

THERE is considerable evidence in the literature<sup>1, 2</sup> that Coramine (Ciba), a 25 per cent aqueous solution of the diethylamide of pyridine beta carboxylic acid, has been established as a valuable agent in the treatment of cerebral and respiratory depression due to poisoning by the barbiturates, avertin, alcohol, opiates, etc. There is little conclusive evidence concerning its action on the circulatory system<sup>2, 3</sup> or on the respiratory distress of heart disease, although there appears to be a definite impression that benefit does follow its use. Objective evidence to explain the symptomatic response has not been striking.

A number of independent observers<sup>4, 5, 6, 7</sup> and others have shown, by animal experimentation, that Coramine acts as a coronary dilator, and Stoland and Ginsberg<sup>4</sup> have concluded that in dogs small doses are effective as a general vascular dilator while large doses are more effective as a coronary dilator. Such findings in animals with apparently healthy vascular tissue unfortunately can not be transferred directly to humans with diseased arteries. Wright<sup>8</sup> has been unable, using Coramine, to demonstrate appreciable changes in the peripheral vascular circulation in man in spite of the fact that Massart<sup>9</sup> concludes from observations on the intact dog that this drug causes a generalized arterial relaxation.

Other measurable objective data are meager. Frommel<sup>10</sup> found in electrocardiographic studies a shortening of conduction time (P-R interval) in frogs, guinea pigs and rabbits when non-toxic doses were used. Eisner<sup>11</sup> studied the effect on conductivity in clinical material and reported no change with Coramine. Cowan<sup>12</sup> believes he obtained an increased voltage in the first ventricular complex, but notes variable changes in the T-waves.

Concerning the blood pressure and pulse rate changes there have been

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\* Read at the Cleveland meeting of the American College of Physicians, April 4, 1940.



hyperpnea, "burning" sensation and excitement, which preceded a fall in pressure. Two cases (4 and 15), with slight immediate symptoms, showed a prompt drop, while the remaining case with moderate reaction to Coramine maintained an unchanged pressure for five minutes from the onset of injection before a fall was noted. Two patients (case 5 (figure 2) and case 15) with marked Cheyne-Stokes respiration gave two readings—one during

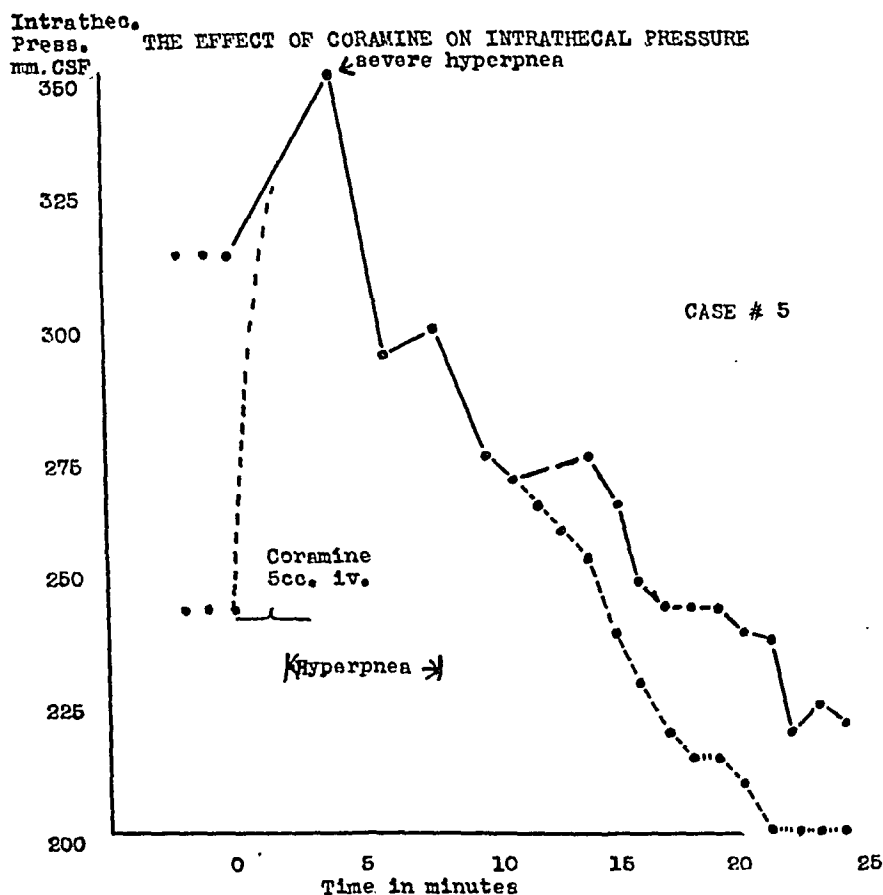


FIG. 2. Case 5: The initial basal intrathecal pressure in this patient with Cheyne-Stokes respirations is 315 mm. of spinal fluid during the hyperpneic phase and 245 mm. during apnea. Coramine (5 c.c.) intravenously, given over a period of three minutes, caused a sharp increase in pressure, along with abolishment of periodic breathing and attended with marked excitement, severe hyperpnea, burning sensation and free perspiration for a few minutes. The pressure then fell sharply. After 12 minutes respirations again began to alternate between quiet (interrupted lines) and exaggerated (solid lines) phases, although there were no periods of apnea for one hour.

apnea and the other during hyperpnea. Periodic breathing in these cases was replaced, during or just after the administration of Coramine, by regular hyperpneic respirations, but 5 to 12 minutes later there was a cyclic variation between quiet and exaggerated phases without periods of apnea.

In spite of the tendency to return to Cheyne-Stokes breathing (figure 2) as evidenced by an alternation between quiet and exaggerated phases, the

TABLE I  
Effect of Coramine in Treatment of Cardiac Respiratory Distress

Case Number	Diagnosis	Type of Distress	Dosage	Results	Effect of Withdrawal	Again Started Coramine	Effect
1	Art. scl. hypertension; CE; frequent P.B.; MI; Class IV	Paroxysmal nocturnal dyspnea, 7-11 attacks q.n.	3 c.c. p.o. 5 i.d. for 4 days	Marked symptomatic response, and attacks reduced to 3	Attacks increased to 7-8-14 on successive nights	3 c.c. p.o. 5 i.d. for 10 days	Diminishing attacks on successive nights 8, 8, 8, 4, 0, 0, 0, 0, 0
2	Art. scl. hypertension; CE; premature beats; MI; Class IV	Cheyne-Stokes (Cardiac psychosis)	5 c.c. i.m. q 4 h. 4 days	Slept 1st night. In 24-48 hrs. normal breathing for $\frac{3}{4}$ -2 hrs. after each dose. After 48 hrs. normal resp.	No recurrence of Cheyne-Stokes in 2 days. Patient died with coronary closure		
3	Art. scl. hypertension; CE; gallop rhythm; MI; Class IV	Cheyne-Stokes. (No orthopnea)	3 c.c. p.o. 5 i.d. 7 days, 3 c.c. i.m. 4 days	Cheyne-Stokes not controlled until 6th day. Reverted to Cheyne-Stokes on 8th day with increased failure			
4	Rh.H.D.; CE; AS, AI, MI, gallop rhythm; Class IV	Paroxysmal nocturnal dyspnea. Cheyne-Stokes	5 c.c. i.m. 7:30 p.m. and 10 p.m.	Slept without attack	Cheyne-Stokes recurred next day. Increased dyspnea	5 c.c. i.v. and 4 hrs. later 5 c.c. i.m.	No further respiratory distress
5	Art. scl. hypertension; CE; premature beats; MI; Class IV	Sept. 1938, paroxysmal dyspnea Nov. 1938 Cheyne-Stokes (Cardiac psychosis)	3 c.c. p.o. 4 i.d. 15 days  3 c.c. p.o. 4 i.d. 22 days	After 24 hrs. fewer attacks. After 48 hrs. complete relief  No relief			

20 minutes, although the degree of fall was not marked. Figure 3 graphically represents the response in a patient with Cheyne-Stokes respirations (compare with figure 2).

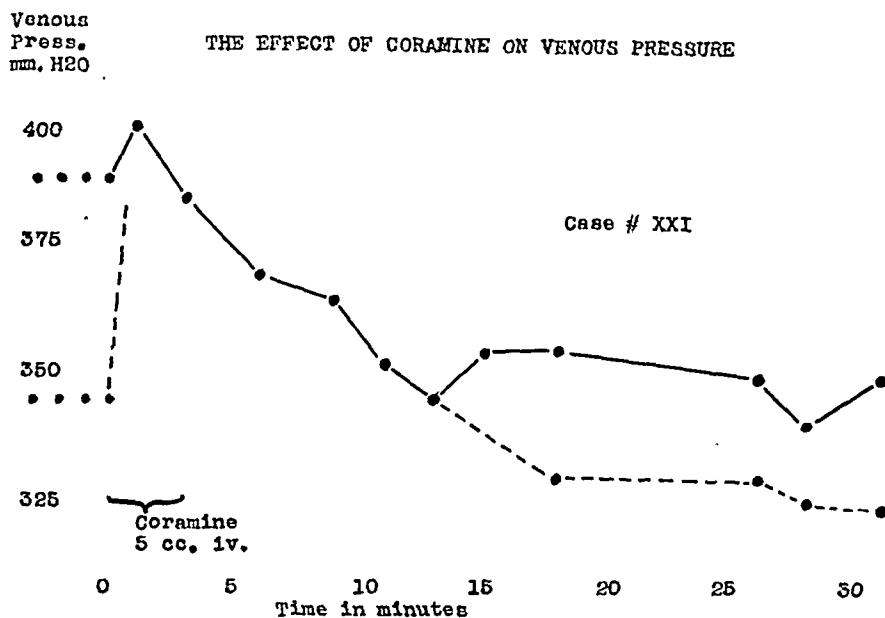


FIG. 3. The initial basal venous pressure in this patient with Cheyne-Stokes respirations is 390 mm. sodium citrate during the hyperpneic phase and 345 mm. during apnea. Coramine (5 c.c. i.v.) quickly abolished periodic breathing and the pressure gradually fell. After 13 minutes respirations again began to alternate between quiet (interrupted lines) and exaggerated (solid lines) phases, although there were no periods of apnea during the experiment.

#### ABSTRACT OF CASES TREATED FOR RESPIRATORY DISEASES

*Case 1.* W. W., colored male, aged 64, a known cardiac with arteriosclerotic hypertensive cardiovascular disease, admitted Dec. 22, 1938 with dyspnea, orthopnea, cough, edema and epigastric discomfort. Considerable improvement followed routine treatment, but nocturnal dyspnea recurring 7 to 11 times each night remained a distressing symptom and was only fairly well controlled with opiates. We first saw him on Jan. 29, 1939, and found him to have moderate dyspnea and orthopnea, with slight engorgement of the neck veins. Heart rate 64, rhythm irregular with frequent premature contractions, cardiac enlargement, mitral insufficiency, blood pressure 210/100 with pulsus alternans. Few râles at lung bases. Liver down 4 cm. and slightly tender. Slight sacral edema. Digitalis gr. iss continued as before and Coramine 3 c.c. per os five times daily, started. During the first 48 hours there was little change except for the patient's statement that the attacks were much less severe. During the next two days attacks recurred only four and three times at night, dyspnea was much less marked, appetite improved and the patient said he felt much better. Inadvertently no Coramine was given for the next three days and symptoms recurred, the number of attacks of paroxysmal nocturnal dyspnea increased to 7, 8, and 14 on successive nights, dyspnea became constant and appetite failed. Upon returning to Coramine 3 c.c. five times daily for the next 10 days (Feb. 8-17 incl.) attacks diminished on successive nights to 8, 8, 8, 4, 0, 0, 0, 0, 0, 0, while relief of disturbing dyspnea and return of appetite were more prompt. The patient was allowed out of bed on Feb. 14 and left the hospital on Feb. 20, symptomatically recovered.

of them reverted to their respiratory distress within 8 hours to 3 days; the remaining case (2) died from coronary closure two days after treatment was interrupted. Five of these patients were then given Coramine again and relief of distress was soon evident. The delayed response in case 1 would throw doubt on the correlation between the relief of paroxysmal dyspnea and treatment, but we are inclined to credit Coramine in view of a more prompt relief of disturbing dyspnea, return of appetite, etc. In cases 5 (Sept. 1938), 5 (Feb. 1939) and 6 improvement was evident following the use of Coramine but there are no adequate controls so that the results are merely suggestive. A review of these cases shows that in five trials there were favorable responses which were controlled, in five trials there was evident benefit but control was unsatisfactory, while the response was negligible in the remaining three trials.

#### EFFECT ON SIGNS OF CARDIAC EFFICIENCY

A second group of patients with moderate congestive heart failure were studied objectively to observe if any notable change resulted following the use of Coramine given orally, which might reflect cardiac efficiency. None of this group had received digitalis during the month preceding these observations, and four or more days of bed rest with sedation and limited measured fluid intake were allowed. Record was made of variations in the arterial blood pressure, blood circulation time (using saccharin in 100 per cent solution—arm to tongue time), pulse rate, vital capacity and electrocardiograms; evidence of diuresis was noted as indicated by volume output of urine, in relation to constant intake, and by change in weight. Readings were made at intervals of not more than four days. Table 2 explains these findings. Allowing for the influence of bed rest, there has been no evidence of constant improvement in cardiac efficiency with Coramine.

#### EFFECT ON INTRATHECAL PRESSURE

W. G. Harrison, Jr.<sup>16</sup> demonstrated that the intrathecal pressure of patients with congestive heart failure was greatly elevated; that the venous pressure showed a similar elevation above normal; and that changes in the pressure of one are usually paralleled by changes in the other. By withdrawal of sufficient spinal fluid to lower considerably the intrathecal pressure, he was able to observe a resulting lowering in the venous pressure in 8 out of 13 cases, and in a larger number there was evident symptomatic improvement. Following the example of Greene, Paul and Feller<sup>17</sup> who showed changes in intrathecal pressure and venous pressure as a result of treatment with theophyllin with ethylene-diamine (aminophyllin), we are studying cases to observe the response to the use of Coramine. Intrathecal pressure changes have been recorded on seven patients. In each case the patient was placed on his side on a stretcher with the head elevated on three pillows, the intrathecal space was entered in the lumbar region and the pressure repeatedly

1934 because of arteriosclerotic hypertensive heart disease, and positive Wassermann. Admitted to the hospital 10 times because of decompensation. On admission Sept. 7, 1938, patient was decompensated, with marked orthopnea and dyspnea, gallop rhythm, venous engorgement, and an electrocardiogram that showed a left bundle branch block, first degree heart block (PR 0.22 sec.) and premature ventricular contractions. Blood pressure 130/80 with pulsus alternans. Improvement was noted until Oct. 1 when gallop rhythm became more marked and he complained of frequent attacks of paroxysmal dyspnea, particularly during the late afternoon and night. On Oct. 4 Coramine 3 c.c. four times a day was started p.o. Less frequent attacks occurred on the fifth, and on the sixth dyspnea had been relieved and his general condition improved so that he was allowed out of bed on the twelfth. Coramine stopped on the nineteenth when the patient was discharged.

Readmitted on Nov. 15 with Cheyne-Stokes respirations and cardiac psychosis. Gradual general improvement noted although Cheyne-Stokes persisted. Coramine 3 c.c. p.o. four times a day given between Dec. 13 and Jan. 4, 1939 failed to improve respiratory distress. Improvement continued, however, so that he left the hospital on Feb. 2.

Feb. 9 in O.P.D. again in failure with marked Cheyne-Stokes respirations, gallop rhythm, and irregular pulse due to auricular, nodal and occasional ventricular premature contractions. Coramine was given in teaspoonful doses four times daily. At the next O.P.D. visit one week later (Feb. 16) there was no evidence of Cheyne-Stokes although dyspnea was still marked, and there was no return toward compensation. Symptomatically the patient stated that he had obtained definite relief of marked respiratory distress about 24 hours after starting this medication. A week later (Feb. 23), having continued the same dose of Coramine, the patient presented himself with evidence of increased edema, but dyspnea was only minimal and gallop rhythm had disappeared. Between Feb. 23 and March 9 Coramine in drachm doses was taken three times a day, but decompensation was marked, Cheyne-Stokes again present, dyspnea marked and coupled rhythm present (from digitalis toxicity).

Admitted March 9 and intrathecal pressure recorded as noted in figure 2. Five c.c. of Coramine intravenously converted Cheyne-Stokes to regular hyperpneic rhythm for about 10 minutes, followed by cyclic breathing, but no periods of apnea for one hour.

On March 15 as coupling had not been observed for three days, and because patient showed signs of increased failure and periodic breathing continued, digitalis gr.  $1\frac{1}{2}$  daily and Coramine 4 c.c. p.o. five times a day were started simultaneously. On March 16 respiratory rhythm was again regular. Coramine was stopped on March 20 and patient returned to periodic breathing on March 23. Relief of congestive failure followed the later use of intravenous mercurial diuretics, and was not influenced by Coramine.

*Case 6.* S. N., aged 68, white female, with hypertensive arteriosclerotic cardiovascular disease had been considerably incapacitated for over a year. Electrocardiograms showed left bundle branch block. On three separate occasions during a nine month period of follow, she had periodic breathing and each time responded to 25 drop doses of Coramine p.o. four times a day, improvement and cessation of Cheyne-Stokes occurring within 24 to 48 hours. During the last two months of follow she continued taking Coramine in 25 drop doses three times a day regularly without return to abnormal respiratory rhythm.

*Case 7.* G. M., colored male, aged 53, admitted March 3, 1939, having had progressive signs and symptoms for three months, viz: epigastric discomfort, dyspnea, and palpitation on exertion; edema noted especially in the past week and during this time he has had hallucinations, delusion and excitability. On admission patient showed evidence of cardiac disease, arteriosclerotic, hypertensive, enlargement, gallop

TABLE III  
Effect of Coramine \* on Intrathecal Pressure

Case Number	Diagnosis	Art. Blood Pressure	Intrathecal Pressure †	
			Before Coramine	After Coramine
4	Rheumatic AS, AI . . . . .	170/65	225	190
5	Art. scl. . . . .	140/80	315 (245)	220 (200)
14	Luetic AI . . . . .	160/60	190	132
15	Luetic AI . . . . .	184/70	275 (245)	192 (175)
16	Art. scl. hypertension . . . . .	230/140	435	370
17	Art. scl. hypertension . . . . .	170/95	140	118
24	Art. scl. hypertension . . . . .	144/102	225	180

\* Dosage—5 c.c. intravenously.

† Intrathecal pressure in mm. spinal fluid.

(—) Indicates readings during quiet phase of cyclic breathing.

Each case showed an initial elevation of the intrathecal pressure. Fall in pressure to lowest figure occurred between 10 to 20 minutes after 5 c.c. of Coramine intravenously. The figures in parentheses (—) indicate an alternative reading taken during the quiet phases in two patients with periodic breathing. Case 5 is illustrated graphically (figure 2).

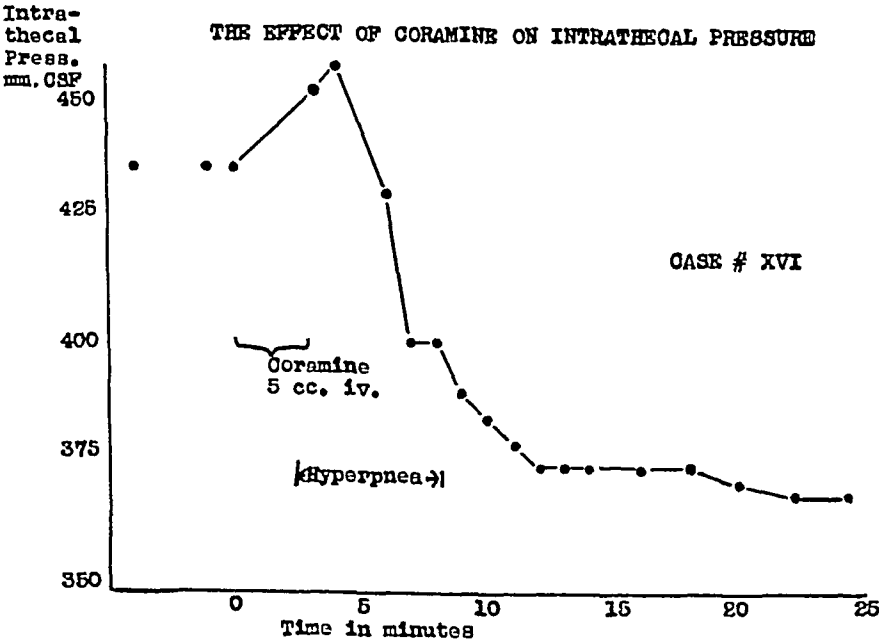


FIG. 1. Case 16: The initial basal intrathecal pressure was 435 mm. of spinal fluid. Coramine (5 c.c.) intravenously given over a period of 3 minutes caused a temporary rise in pressure concomitant with the onset of hyperpnea and a slight sensation to the patient of burning of the face lasting a few minutes. Pressure then fell sharply to 375 mm.

of increased cardiac failure, severe dyspnea and mental confusion. Digitalis, which had previously been prescribed, had not been taken faithfully during the past several months. Arteriosclerosis of the peripheral vessels was extreme, there was no perceptible radial pulse and blood pressure readings could not be made. Cheyne-Stokes breathing was distressing with periods of apnea lasting 30 to 40 seconds. Electrocardiograms showed bundle branch block of the common type. Marked cardiac enlargement. Occasional premature beats and apical systolic murmur. Digitalis was given, and, on the third day of hospitalization, Coramine was started in 4 c.c. doses by mouth, repeated 5 times daily and continued for seven days. Although there was progressive clearing in the sensorium, Cheyne-Stokes breathing persisted, gradually lessening in severity. It was felt that Coramine had not afforded significant relief.

### COMMENTS

Believing from reports in the literature and from our experience, that direct action of Coramine on cardiac efficiency is not marked, we look to the respiratory system for an explanation of a favorable action on the respiratory distress of cardiac disease. It remains a matter of speculation whether such relief results from (1) stimulation of the respiratory center; (2) reduction of intrathecal pressure; (3) relief of cerebral venous engorgement; or from (4) some other unknown factor. The widely accepted theory for the cause of the type of Cheyne-Stokes respiration associated with cardiovascular disease assumes that with a failing circulation there develops a relative anoxemia of the cerebral tissue, the respiratory center becomes depressed and apnea results; carbon dioxide then increases and acts as a respiratory stimulant reinitiating respirations until the carbon dioxide content is sufficiently diminished so that the cycle repeats.

Coramine's ability to stimulate cerebral tissue has considerable support from the numerous studies on denarcotization. CoTui<sup>20</sup> gave lethal doses of procaine hydrochloride cisternally to dogs and with Coramine was able to reduce the mortality. By irrigating the fourth ventricle of one animal with procaine hydrochloride respirations were completely abolished, yet were restored with 10 c.c. of Coramine intravenously, given in two doses of 5 c.c. each. The sweating and restlessness, which we frequently observed after intravenous Coramine, suggest stimulation of nervous tissue, and the transient hyperpnea indicates stimulation of the respiratory center. However, Greene and Heeren<sup>21</sup> do not believe that aminophyllin, an agent which has been shown to control Cheyne-Stokes respirations, acts entirely as a respiratory center stimulant. Their opinion is based on their observations that carbon dioxide, a known central respiratory stimulant, does not convert Cheyne-Stokes to normal breathing but causes a prolongation of the hyperpneic phase (which we find to be so with single large intravenous doses of Coramine) while caffeine 0.5 to 1 gram doses produces a Biot type of breathing. The failure of oxygen to benefit this type of abnormal breathing is of doubtful significance in view of experimental evidence that anoxemia gives a variable response as a respiratory stimulant.<sup>22</sup> Nathanson and Fitzgibbon<sup>23</sup> could not relieve Cheyne-Stokes breathing with the use of benze-

pressure continues to fall, suggesting little correlation between the fall of pressure and the type of breathing. Two cases with Cheyne-Stokes breathing that responded in this manner to Coramine, failed to be relieved of their periodic breathing by withdrawal of large amounts of cerebral spinal fluid with considerable reduction of pressure.

### EFFECT ON VENOUS PRESSURE

Venous pressure determinations have been made on seven subjects using the apparatus described by Moritz and von Tabora<sup>18</sup> for continuous readings. Because of orthopnea the patients' heads were elevated 30 degrees above the horizontal; the arms were abducted to 45 degrees and supported in a comfortable position. There was no effort to be exact with the reference point for zero readings, although this point was roughly estimated.<sup>19</sup> Readings were repeatedly made until there was no variation for 10 minutes and then Coramine was given intravenously in doses of 5 c.c. over a period of 3 minutes. (Table 4).

TABLE IV  
Effect of Coramine \* on Venous Pressure

Case Number	Diagnosis	Art. Blood Pressure	Venous Pressure †	
			Before Coramine	After Coramine
5	Art. Scl. ....	140/80	205	156
18	Art. Scl. ....	136/80	214	185
19	Luetic AI. ....	165/50	94	Same
20	Luetic Aortitis. ....	140/80	170	145
21	Art. Scl. ....	110/90	380 (345)‡	340 (323)‡
22 <sup>1</sup>	Art. Scl. ....	195/115	164	Same
23	Art. Scl. ....	230/145	142	115

\* Dosage—5 c.c. intravenously.

† Venous pressure in mm. sodium citrate.

‡ Readings during quiet phase of respirations.

<sup>1</sup> Cheyne-Stokes. Respiratory rate 9–10 min., azotemia.

Following the intravenous use of Coramine (5 c.c.) there has been a fall in venous pressure in five of the seven cases, the maximum fall reached within 20 minutes. In two cases (19 and 22) there was no appreciable change. Case 22 died two days later with renal insufficiency. Case 21, with periodic breathing, is graphically illustrated (figure 3).

It is noted that two patients (cases 19 and 22) showed no change in pressure. One of these cases (19) had a normal venous pressure, while the other (22) had Cheyne-Stokes respirations, with a rate of 9 to 10 per minute, marked azotemia, and died two days later of renal insufficiency. This patient's respirations were not altered in rate or depth. The remaining cases did respond with a fall in pressure reaching the minimum level within



vagus nerves. That cerebral blood flow is subnormal in hyperpneic cardiac patients is supported by McMichael<sup>31</sup> from data on jugular vein oxygen content. There is little evidence from the present data that fall in venous pressure is striking enough to afford relief of cerebral engorgement or otherwise improve blood flow.

### SUMMARY AND CONCLUSIONS

It has been demonstrated that Coramine may have a beneficial action on the abnormal respirations associated with cardiac disease. Dramatic responses, however, are not usually found from oral doses, but rather a slow progressive improvement—usually one to three days elapse before the optimum benefit is realized. A more prompt but transient response follows its use intravenously and may be attended (as used in 5 c.c. doses) by symptoms from widespread cerebral stimulation.

Cardiac efficiency was not shown to be constantly improved from prolonged oral use of Coramine.

Decline in intrathecal pressure, following its intravenous administration, was observed and, to a less constant or striking degree, a decline in venous pressure. That these pressure changes are directly related to the improvement noted is considered doubtful. The present evidence points to Coramine's stimulation, as a chemical agent, of the respiratory receptors, either peripherally or centrally.

Further studies are indicated.

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*Case 2.* J. A., colored male, aged 60, entered the hospital on Feb. 10, 1939 complaining of substernal pain radiating to the neck and left arm, increased with exertion. Attacks lasting 5 to 10 minutes have been more severe and frequent in the past six weeks. Had shown progressive evidence of myocardial failure. On admission he was found to have cardiac disease, arteriosclerotic and hypertensive, enlargement, premature beats, mitral insufficiency, class 4, this picture being complicated by cardiac psychosis, and questionable presence from history and electrocardiogram of anterior myocardial infarction (proved at necropsy). Digitalization started slowly. On the second day following admission (Feb. 12) Cheyne-Stokes respirations appeared irregularly, patient was more confused and temperature rose due to broncho-pneumonia. On Feb. 13 Cheyne-Stokes respirations were constant. On Feb. 16 Coramine 2 c.c. given intravenously and a 5 c.c. dose intramuscularly, the latter being repeated every four hours. After the third dose respirations became regular and the patient slept. He remained confused but passed a more restful night. On Feb. 17 it was observed that each dose of Coramine would control the respirations for periods of  $\frac{3}{4}$  to 2 hours after each injection; the remainder of the time they were of the Cheyne-Stokes type. On Feb. 18 and Feb. 19 no periods of Cheyne-Stokes were observed and the medication was then stopped. Cheyne-Stokes did not recur on Feb. 20 but the patient died suddenly on that day.

*Case 3.* W. S., colored male, aged 69, a known arteriosclerotic hypertensive cardiac with cardiac enlargement, mitral insufficiency, gallop rhythm and periods of paroxysmal (nodal) tachycardia, class 4, Wassermann positive. Entered on Jan. 29 with marked dyspnea and Cheyne-Stokes type respirations. Blood pressure 180/100. Vessels markedly sclerotic. Neck veins engorged, free fluid in right pleural cavity, 2 plus sacral edema, abdomen distended. Started on Coramine on Jan. 30, 3 c.c. p.o. five times daily. On Feb. 6, Cheyne-Stokes was replaced by regular breathing and dyspnea less marked. However, the patient became more confused mentally. The day following he reverted to Cheyne-Stokes in spite of continued medication. On Feb. 8, the oral dose was replaced by 3 c.c. i.m. five times and this was continued through Feb. 11 without significant benefit. After an additional  $2\frac{1}{2}$  weeks in bed Cheyne-Stokes and sensorium cleared and the patient made a complete symptomatic recovery. It is worthy of note that for most of the course with Cheyne-Stokes respirations, orthopnea was not a marked feature, the patient lying flat in bed without apparent added discomfort.

*Case 4.* F. S., white male, aged 42, known rheumatic fever in early teens, and definite evidence of rheumatic heart disease, cardiac enlargement, aortic stenosis, aortic insufficiency, and mitral insufficiency. Decompensation caused by severe respiratory infection and cough. When admitted Feb. 16, there was evidence of failure in engorgement of neck veins, râles at lung bases, marked precordial protodiastolic gallop, liver 2 cm. below costal margin and slight ankle edema. His presenting symptom was paroxysmal dyspnea, almost entirely preventing sleep for the past few nights. Digitalization started on admission, and the first night the patient rested after the use of morphine sulphate subcutaneously. Feb. 17 pentobarbital failed to give relief of frequent attacks. Feb. 18 it was noted that Cheyne-Stokes respirations occurred when patient was relaxed. At 7:30 p.m. and again at 10:00 p.m. Coramine 5 c.c. was given intramuscularly and the patient slept through the night without evidence of Cheyne-Stokes or dyspnea. On Feb. 19 in the afternoon, paroxysmal attacks recurred and respirations rhythmically alternated between a quiet and exaggerated phase. Five c.c. of Coramine were given intravenously with rhythm becoming regular and no tendency to Cheyne-Stokes. This dose was repeated intramuscularly four hours later and the patient again had a good night. No further respiratory embarrassment was experienced during his stay in the hospital.

*Case 5.* Wm. Sh., colored male, aged 60, has been followed in our clinics since

# IRON METABOLISM AND ITS RELATIONSHIP TO ANEMIA AND THERAPY \*

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IRON, in the form of an inorganic salt, may be considered as a specific remedy for certain types of anemia and will produce results which are comparable to those obtained by liver extract in the treatment of pernicious anemia. The use of iron as an antianemic remedy is not new but the results which have been obtained in recent years are more striking than in the past and have served to focus attention on this metal. The increased popularity and the apparent increased effectiveness have been due primarily to the administration of adequate amounts of iron to properly selected cases whereas in the past it has frequently been used indiscriminately in all types of "secondary" anemia. The renaissance has been due, therefore, to a better understanding of the pathogenesis of the anemias rather than to any increased effectiveness of the drug itself.

When an adequate amount of iron is not available for hemoglobin formation a hypochromic type of anemia develops which is characterized by microcytosis, hypochromia of the individual erythrocytes, and low color and volume indices. The cause of the deficiency in available iron varies from case to case, and although there are obvious gaps in our knowledge of iron absorption, storage, and utilization, certain facts have been established which serve to explain the pathogenesis of these anemias. Opinions differ as to the amount of iron which is required each day by a normal individual and many types of experiments have been carried out in an attempt to ascertain this level.<sup>† 1</sup> Some observers believe that a diet containing 5 mg. of iron per day is sufficient to maintain a normal iron balance<sup>2</sup> while others believe that larger amounts are necessary. We have shown<sup>1</sup> that a daily iron intake of from 3.81 to 6.76 mg. resulted in a negative iron balance in five individuals whereas when four of these same subjects were given diets containing from 12.22 to 15.53 mg. of iron all were in positive balance. From these results and from further studies on a group of 42 patients it was concluded that the dietary iron intake should be in the neighborhood of 12 to 15 mg. per day to insure adequate iron absorption. It has been shown that not all of the iron which is present in various foods is available for absorption and utilization<sup>3, 4, 5</sup> and this may be taken as another point in favor of the higher dietary iron intake.

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† A complete survey of the literature on the subject of iron requirements is given in reference<sup>1</sup>.

rhythm, class 4. Cardiac psychosis and moderately marked systemic, portal and pulmonary congestion present. Breathing was of the periodic type and orthopnea was marked. He had been taking digitalis prior to admission; this was increased and continued. Coramine 4 c.c. intramuscularly was started on the day following (patient refused everything by mouth) but lacking coöperation it was given irregularly and stopped on March 7, periodic breathing persisting. Over a period of three weeks the patient made gradual improvement, but on March 31 dyspnea became more marked and he again became confused. Cheyne-Stokes reappeared on Apr. 2 and this was more marked on April 5. On that day 5 c.c. of Coramine were given slowly intravenously, and Cheyne-Stokes breathing immediately replaced by hyperpneic regular breathing for about 5 minutes, following which breathing alternated between quiet and exaggerated phases. Periods of apnea were observed  $\frac{1}{2}$  hour later. Then Coramine 3 c.c. p.o. was started every three hours. The next day (April 6) there was no apparent change. An April 7, for variable periods following medication, respirations were regular and the patient stated that he was breathing easier. On April 8 respirations remained regular and there was no evident dyspnea. Breathing was easy and regular on April 9 and April 10. On April 10 Coramine was discontinued and two days later on April 12 Cheyne-Stokes breathing was again distressing. At noon on April 12 Coramine was resumed as before. Breathing again became regular on the afternoon of April 13 and was attended with symptomatic relief.

*Case 8.* T. F., aged 57, white male, admitted to the hospital Nov. 10 because of attacks of nocturnal dyspnea and cardiac asthma recurring with increasing frequency and severity for the past two months. On examination he was orthopneic, dyspneic, somewhat cyanotic with pulmonary emphysema and râles at the lung bases. Cardiac enlargement with diminished heart sounds and apical systolic murmur was noted. Blood pressure 200/114. Peripheral vessels markedly sclerotic and tortuous. Liver down 3 cm. No peripheral edema. Oxygen and narcotics gave some relief but did not prevent attacks. Coramine medication was started on Nov. 14 after four days of the above treatment, and the drug was given in doses of 4 c.c. five times daily. There was gradual improvement progressing to complete relief in three days. Slight nausea was noted after each dose of Coramine. On Nov. 18 this medication was discontinued and attacks of paroxysmal dyspnea returned two days later (Nov. 20). Coramine again given this time in 3 c.c. doses 5 times daily with relief within 15 hours. On Dec. 3 medication again stopped, and on Dec. 4 symptoms reappeared, but were quickly relieved by further medication.

*Case 25.* J. Q., a 69-year old male carpenter, with arteriosclerotic heart disease who suffered a myocardial infarction in the spring of 1939. Admitted Dec. 1939 because of heart failure and paroxysmal nocturnal dyspnea. Had been digitalized and maintenance dose was continued. Improvement was progressive until Jan. 6, 1940 when he had a cerebral accident, following which failure increased. On Jan. 21, fever rose to 101° F. due to broncho-pneumonia. On Jan. 23 Cheyne-Stokes respirations were noted and two days later this was distressing with periods of apnea lasting 30 to 35 seconds. Coramine (4 c.c. per os) was then started and repeated 5 times daily. Within 24 hours respirations were converted to quiet normal breathing, even during sleep, and so this medication was stopped. Temperature now normal. Eight hours later Cheyne-Stokes reappeared and on Jan. 28 Coramine was again given as before, and on the twenty-ninth normal breathing was present. Because of hiccoughs and nausea the dose of Coramine was reduced to 3 c.c. five times daily with relief. Nausea recurred on Feb. 4 and treatment again was discontinued. Cheyne-Stokes again present on Feb. 6, but as this was not distressing, no further Coramine was used. Two days later (Feb. 8) respiration became normal and patient continued to improve without further treatment.

*Case 26.* J. E., a 74-year-old colored man, entered the hospital because of signs

metabolized by the body is quite constant and does not vary significantly under ordinary circumstances.

The third factor influencing the iron requirement is the formation of new iron-containing tissue. This feature is important in the mother during pregnancy since the fetus at the time of birth contains in the neighborhood of 350 mg. of iron,<sup>15</sup> all of which must have been obtained from the maternal organism. It is obvious that the iron intake of the mother must be adequate, and the absorption efficient, in order to supply the fetal requirements. Not infrequently the maternal iron supplies are significantly depleted at this time. A large amount of iron is needed by an infant during the period of rapid growth and unless the iron reserves at birth are adequate to meet these demands an iron deficiency will result since the iron intake is low during this period. The demand for iron continues high during childhood<sup>16</sup> but is particularly great at the time of puberty and it has been estimated that the need for iron is as great at that period as during pregnancy.<sup>17</sup>

With these features of iron metabolism in mind we may examine the common types of hypochromic, iron deficiency anemias. The hypochromic anemia of infancy is particularly common in premature infants in whom growth is rapid, the demand for iron is great, and the iron stores not as large as normal. It is also common in the case of twin pregnancies. Such an anemia may also develop in normal children who have an adequate iron reserve at birth but whose diet is low in its iron content, as is the case with the prolonged use of cow's milk without supplementary foods. A nutritional anemia in adults may result from a long-continued low iron diet which results in a depletion of the iron reserves but in our experience such anemias are not severe, as a rule, unless there is an associated achlorhydria to further interfere with iron absorption. Classical cases of chlorosis are seldom encountered today although mild hypochromic anemias are common during adolescence. These are apparently due to the excessive demand for iron at this time, the onset of menses and in many cases a diet low in iron-containing foods.

The anemia of chronic hemorrhage results from the loss of iron at a more rapid rate than it can be replaced from the dietary intake. This ultimately results in a depletion of the iron stores and a reduction in the rate of hemoglobin regeneration. The hypochromic anemia of pregnancy is a result of several factors.<sup>18</sup> The fetal demand for iron is a severe drain on the maternal stores and is one of the essential features, but not all pregnant women develop this type of anemia so that some additional cause must be found. The diet may be inadequate in its iron content either through the patient's inability to procure proper food or because of persistent nausea and vomiting or a somewhat abnormal appetite. Of greater importance is the achlorhydria or hypochlorhydria which is present in practically all of these cases and prevents the absorption of sufficient iron to supply the demands.

Idiopathic hypochromic anemia occasionally has its onset during pregnancy or follows repeated pregnancies in patients who are unable to make up

drene sulphate (10 mg. intravenously) nor with Coramine in 2 c.c. doses, although these are credited cerebral stimulants, while theophyllin proved of value. In their report, one of three cases was temporarily relieved with caffein sodio-benzoate in doses of 0.75 gram. With accumulating knowledge of the physiology of respirations<sup>24</sup> we know that receptors for reflex respiratory center stimulation are present (carotid sinus, arch of the aorta, alveoli, etc.) and that these may be affected by changes in the carbon dioxide content of the blood, by simple rise in pressure, acting as a physical stimulus,<sup>22</sup> by ischemia of the carotid body<sup>22, 25</sup> and by stimulation with chemical agents other than physiological agents.<sup>26, 27, 28</sup> Heymans, Bouchaert and Dautrebande<sup>26</sup> showed that cyanides, nicotine, lobeline, etc., act on these receptors to give a reflex hyperpnea and that in small doses these substances do not directly stimulate the respiratory center. Wright<sup>27</sup> confirmed these findings with a large group of respiratory stimulants, and he emphasizes that, although the peripheral receptors are the more sensitive to most of the agents, direct stimulation of the respiratory center can be accomplished by sufficient concentrations of the drugs. This has been shown to be the case with Coramine by Zunz and Tremonti<sup>28</sup> on animal preparations.

That changes in intrathecal or venous pressures may be of significance is suggested by the upright position assumed by patients with severe dyspnea. Harrison<sup>16</sup> had noted a relationship between cardiac failure and increase of intrathecal pressure, and observed a higher cisternal pressure in the recumbent than in the sitting posture and believed this to be the mechanism of orthopnea. Greene, Paul and Feller<sup>17</sup> found that theophyllin with ethylenediamine (aminophyllin) given intravenously produced a decline in the intrathecal and venous pressures, and that the improvement in dyspnea and conversion of Cheyne-Stokes respirations to a regular rhythm was related to the decline in pressures, suggesting that this might be the mechanism for relief. However, glucose in 50 per cent solution given in 50 to 200 c.c. injections, failed to relieve Cheyne-Stokes<sup>21</sup> although this procedure lowers the intrathecal pressure. We have observed that Coramine given intravenously in single doses of 5 c.c. only temporarily alters Cheyne-Stokes breathing, although a definite reduction of the intrathecal pressure is seen. Further, as review of figure 2 will show, there is a continued fall of pressure in spite of the recurrence of respirations alternating between quiet and exaggerated phases, indicating that the type of respiration has little relation to the change in pressure. Simple drainage of cerebral spinal fluid, to lower the intrathecal pressure, has failed to relieve periodic breathing in patients whose respirations are temporarily altered with intravenous Coramine.

Ernstene and Blumgart<sup>29</sup> noted an association between an elevated venous pressure and orthopnea and, in their opinion, this increased pressure causes an impairment of circulation to the respiratory center to produce orthopnea. Harrison et al.<sup>30</sup> demonstrated that elevation of venous pressure or intrauricular pressure causes reflex stimulation of breathing, the reflex presumably arising in the heart or the great veins and the impulses carried by the

depend wholly on their solubility. Moore<sup>21</sup> has demonstrated an increase in the serum iron after the oral administration of an iron salt and the serum iron curve is higher after a ferrous than after a ferric salt. When a reducing agent is given with a ferric salt, however, the serum iron is increased to the same height obtained with a ferrous salt. His results suggest that iron is absorbed largely, if not entirely, in its ferrous form.

Since the iron content of the usual dose of an inorganic salt is much greater than can be accounted for by the iron used in new formed hemoglobin there is no adequate explanation for the greater effectiveness of massive doses as compared to smaller amounts. For this reason balance studies were carried out in an attempt to ascertain the fate of the ingested iron with various doses of an inorganic iron salt.

Iron and ammonium citrates, 3 grams per day yielding approximately 500 mg. of elemental iron, was administered to a group of patients with hypochromic anemia<sup>22</sup> and it was found that 67.4 per cent of the iron was excreted and 32.6 per cent was retained by the body (chart 2). Only 2 per

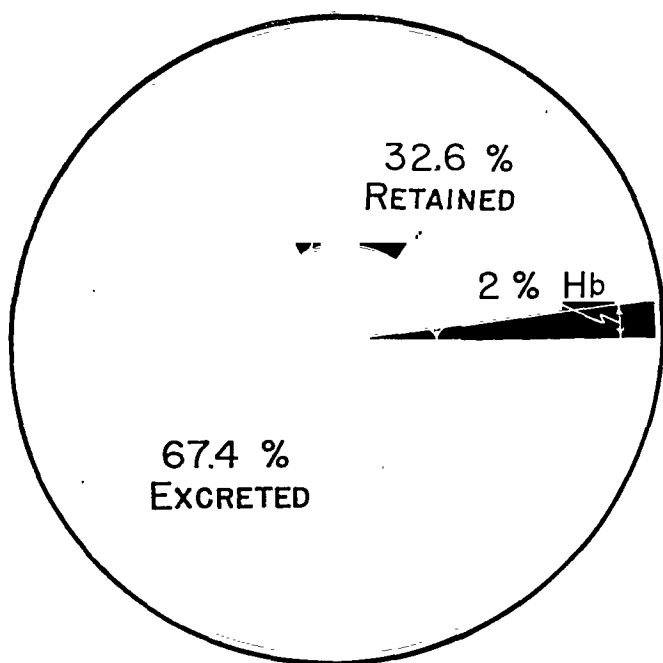


CHART II. Retention and utilization of iron. 500 mg. of iron per day as iron and ammonium citrates (3 grams). A very large amount of iron is retained.

Daily iron intake: 514 mg.

Excreted: 364.4 mg.—67.4%.

Retained: 167.5 mg.—32.6%.

Utilized as hemoglobin: 10.3 mg.—2%.

Average values from 10 cases.

cent of the ingested iron was used immediately in hemoglobin formation and no correlation was found between the amount of iron retained and the amount of hemoglobin regenerated. Exceedingly large amounts of iron continued to be retained with prolonged administration of the drug and if

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iron, it had no effect on the retention of iron from iron and ammonium citrates.<sup>11</sup> Iron and ammonium citrates were administered intramuscularly to a small group of patients and although the iron was retained there was no significant hemoglobin response although subsequent oral administration of iron produced a satisfactory response in two of the patients.<sup>27</sup>

It is to be noted in chart 3 that even when small doses of iron and ammonium citrates were administered there was a daily iron retention of 53.7 mg. and of this, only 16.6 mg. were used in hemoglobin formation. This produced a daily hemoglobin gain of 0.1, 0.15, and 0.08 grams per 100 c.c. of blood in three of the patients and this may be considered as a satisfactory response even though it is not as rapid as the optimum response obtained by Heath with larger doses.<sup>28</sup> The amount of iron retained from this dosage is far in excess of the amount used in hemoglobin formation and would seem to furnish enough iron not only for a satisfactory hemoglobin increase, but also an additional amount to replenish the depleted stores. We have used correspondingly small amounts of several iron salts and the results on hemoglobin regeneration are shown in chart 4. The results with iron and am-

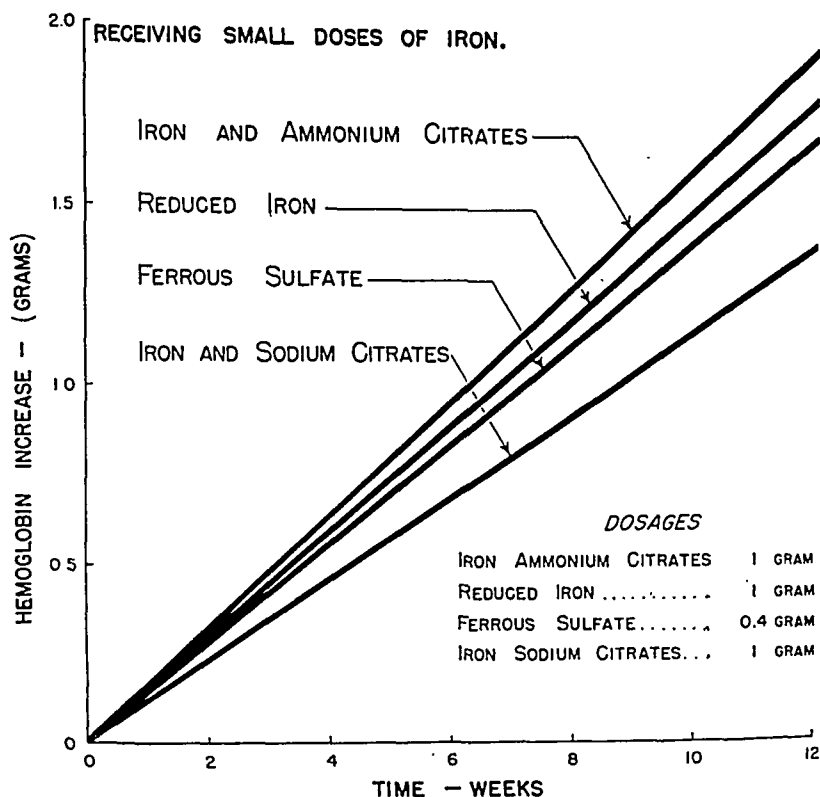


CHART IV. Comparative effects of various iron preparations showing the average hemoglobin increase for four groups of patients with mild anemia receiving small doses of iron.

monium citrates were obtained on 11 patients with an average initial hemoglobin of 11.3 grams. For the other drugs, there were six cases that received *Ferrum reductum* with an initial hemoglobin of 11.1 grams, seven

The acidity of the gastric juice plays an important rôle in the absorption of iron from the gastrointestinal tract and achlorhydria appears to be a more important factor in producing an iron deficiency than does a low iron intake alone. The frequency with which an achlorhydria is found associated with hypochromic anemia has been repeatedly emphasized in clinical reports,<sup>6, 7, 8, 9, 10</sup> but in order to obtain more definite information on this feature iron balance studies were carried out on a group of patients.<sup>11</sup> In 11 patients with achlorhydria who received from 9 to 13 mg. of iron per day (average 10.86 mg.) there were 8 in negative balance and the average daily balance for the entire group was — 4.38 mg. In 15 patients with free hydrochloric acid in their gastric contents and with an average daily iron intake of 11.85 mg. there were only 5 in negative balance while 10 retained iron. The average daily retention for the 15 patients was + 1.02 mg. These results show that less iron is retained from the dietary iron intake when achlorhydria is present and it is obvious that under these circumstances the iron intake must be greater than in a person with a normal gastric acidity if an iron deficiency is to be prevented.

There are three primary factors which determine the iron requirement of an individual: the loss of hemoglobin iron by hemorrhage, the elimination of non-hemoglobin iron, and the formation of new iron containing tissue. The loss of iron through hemorrhage from any source will obviously require replacement and if the hemorrhage is continued over a long period of time the available supply of iron in the tissues of the body will become depleted and an iron deficiency will result. The loss of iron during normal menstruation must be taken into consideration in this connection and in determinations on 100 normal women the average loss was found to be 19.54 mg. of iron per period<sup>12</sup> while in a group of patients with frank menorrhagia the loss was found to be as high as 220.15 mg. per period.<sup>13</sup>

A second factor influencing the iron requirement is the elimination of non-hemoglobin iron. It is known that most of the iron is excreted through the gastrointestinal tract but determinations of the iron content of the feces fail to distinguish between that portion which has passed through the intestinal tract unabsorbed and unchanged and that which has been absorbed and reëxcreted into the bowel. The amount of iron excreted in the urine is small and in some balance studies has been ignored entirely. In an attempt to amplify our knowledge on this phase of iron metabolism the urinary iron output in 200 patients, equally divided between males and females, was studied.<sup>14</sup> The excretion varied from 0.08 to 1.63 mg. per day with a normal dietary iron intake and bore no constant relationship to the amount of iron ingested since the administration of large amounts of a soluble iron salt did not significantly alter the amount of iron excreted by this route. Although the amount varied from patient to patient it was quite constant in the same individual even at widely separated intervals. The iron excreted in the urine must represent iron which has been absorbed and, if not utilized, at least has been available for use and these results indicate that the amount

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the iron deficit incurred during that time. A low iron intake occasionally plays a part but is not a factor in all cases. Achlorhydria or hypochlorhydria is a constant finding and by interfering with the absorption of iron is an essential etiological feature. The primary factor in most cases, however, is the loss of iron through profuse menstruation. This excessive blood loss is not usually recognized by the patient so that no evidence of this is obtained from the patient's history. Determinations of the amount of hemoglobin and iron lost by this route in these patients have shown it to be excessive and in only two of the cases studied was the iron retention from the food large enough to compensate for the menstrual loss.<sup>19</sup> Idiopathic hypochromic anemia is essentially, therefore, a chronic hemorrhagic anemia in a patient in whom achlorhydria prevents the absorption of sufficient iron from the diet to replace that which is being lost.

From this analysis of the causative factors in various types of hypochromic anemia the rationale of iron therapy is evident and the reason for the excellent clinical results is obvious. There are, however, many features concerning the mode of action and the storage of iron which are unanswered. It is known that the administration of adequate amounts of various inorganic iron salts is effective in the treatment of these anemias.<sup>20</sup> The commonly recommended dose of these salts is large, as is shown for a few of the most widely used preparations in chart 1. It is recognized that the soluble salts

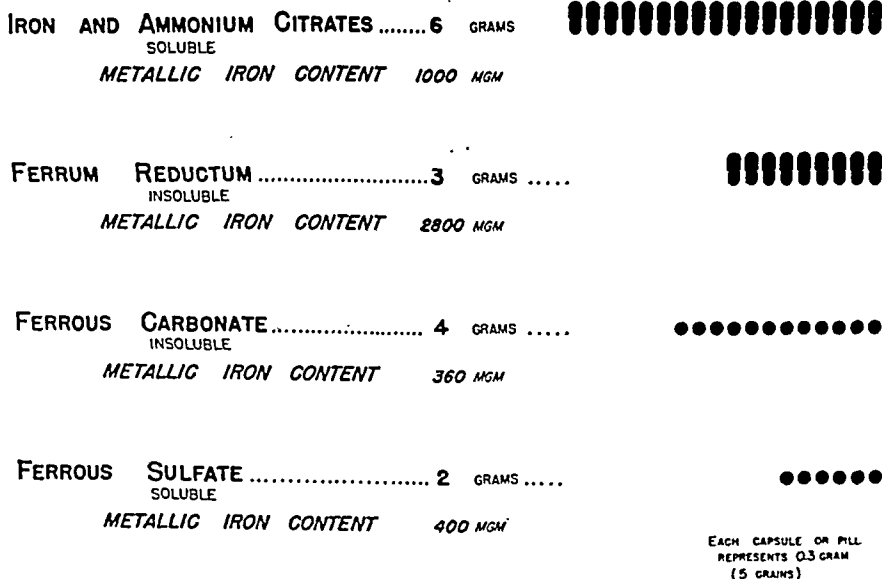


CHART I. Common iron preparations, usual daily dosage. Smaller doses of these drugs will produce a satisfactory hemoglobin response in many patients.

of iron are more readily absorbed and consequently are more effective than insoluble salts when compared on the basis of their elemental iron content. It is also apparent that ferrous are more effective than ferric salts when comparison is made on this basis and their greater effectiveness does not seem to

The fever may be explained as referable to the toxicity of the retained secretions and to the inflammation present. The patient's temperature may be only slightly elevated in the morning, but it may increase rapidly in the afternoon, usually to 101° F. to 103° F. (38.3° to 39.4° C.). A sustained fever in which the temperature rarely decreases to a point below 100° F. (37.7° C.) may be present for days in some cases. The fever is usually accompanied by a leukocytosis. It should be emphasized at this point that febrile episodes, hemoptysis or even purulent sputum do not accompany uncomplicated asthma. The presence or the history of any one or all of these features in an instance of asthma should immediately arouse a suspicion of the presence of bronchostenosis or some other organic complication.

It is noteworthy that 53 per cent of the patients in our series who had bronchostenosis gave a history of pneumonia, and 35 per cent reported a history of pleurisy. Bronchostenosis is not infrequently mistaken for bronchopneumonia because of the severe cough, fever, blood-tinged purulent sputum and also the physical observations of localized congestion referable to the atelectasis which results from the blocked bronchus. Roentgenograms of the thorax also may support the impression of bronchopneumonia and may show a region of pneumonitis or atelectasis. However, after the acute phase subsides, bronchoscopic examination reveals a stenosed bronchus, dilatation and aspiration of which usually relieve the complication promptly. It should be axiomatic, therefore, that a patient who has asthma and who experiences one attack or repeated attacks of "pneumonia" certainly must be suspected of having had stenosis of a bronchus until it has been proved otherwise. This is true of asthmatic children as well as of adults.

The physical signs which may accompany bronchostenosis are secondary to the atelectasis which is present and consist chiefly of suppression of breath sounds and fremitus over the affected region, noted when the affected side is compared with the unaffected side. Less frequently dullness to percussion may be found over the atelectatic region. Careful and repeated examinations of the thorax occasionally will show a definite if not a pronounced difference in physical observations between the involved region in one lung and the uninvolved region in the opposite lung. Persistent unilateral physical signs are of the utmost diagnostic significance because in instances of uncomplicated asthma the physical signs are equal in each lung. In our patients, the stenosed bronchus was always found in the lower half of the lung and most frequently in the apical branch of the lower lobe bronchus, although other branches of the lower lobe bronchus were also often involved. Hence, significant physical observations will most often be found in the lower and posterior portions of the thorax.

The roentgenologic observations most often encountered in instances of bronchostenosis which complicates asthma are usually those characteristic of atelectasis, or less frequently, bronchiectasis. Although the roentgenologic observations sometimes suggest bronchiectasis, the physician must not con-

the analogy can be drawn from animal experimentation, this iron was stored in the liver, spleen, and reticulo-endothelial system. Brock and Hunter<sup>23</sup> and Reimann<sup>24</sup> have likewise demonstrated a large retention of iron. These results do not substantiate the idea that absorbed iron is used quantitatively in hemoglobin formation nor that the amount of iron absorbed can be calculated from the amount of hemoglobin formed.

Further balance studies were carried out with smaller amounts of iron and ammonium citrates (1 gram per day yielding approximately 170 mg. of elemental iron) and the percentage of retention and excretion were similar to those with the larger dose.<sup>25</sup> In these patients 70 per cent was excreted and 30 per cent retained but 9.3 per cent of the administered iron was used immediately in hemoglobin formation (chart 3).

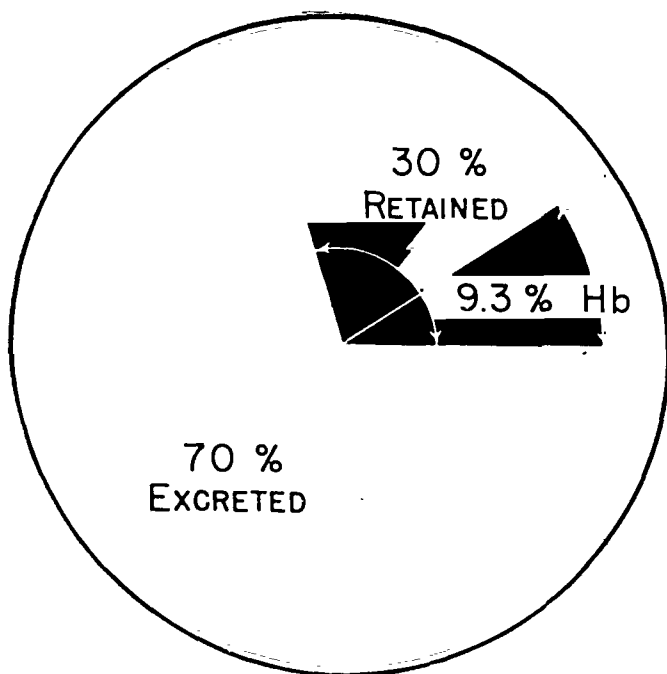


CHART III. Retention and utilization of iron. 170 mg. of iron per day as iron and ammonium citrates (1 gram). A large amount of iron is retained even with this small dosage.

Daily iron intake: 179 mg.  
 Excreted: 125.3 mg.—70%.  
 Retained: 53.7 mg.—30%.  
 Utilized as hemoglobin: 16.6 mg.—9.3%.  
 Average values from 6 cases.

When a liver fraction was added to the iron and ammonium citrates there was no significant alteration in the amount of iron retained nor in the rapidity of hemoglobin formation. With the addition of copper there was a decreased iron retention when small amounts of iron and ammonium citrates were given but the copper had no effect on larger doses of iron. In neither instance was the rate of hemoglobin formation significantly affected.<sup>26</sup> Although an achlorhydria was shown to diminish the retention of dietary

is not doing well, bronchoscopic examination should be strongly considered, since a stenotic bronchus may be the one remaining factor preventing his recovery.

In addition to bronchostenosis caused by localized inflammation such as has been described, the physician may encounter bronchostenosis referable to other causes, such as primary bronchial malignancy complicating allergic asthma, as was found in one of our 60 cases.<sup>2</sup> Although no instances of it were found in our series, the physician might also encounter stenosis of a bronchus or of bronchi caused by tuberculosis, or by ulceration of calcareous material from a lymph node of the hilus into a bronchus, producing the effect of stenosis, or of the presence of a foreign body, or both. In all such instances, a correct diagnosis is crucial and it depends upon bronchoscopic examination, supplemented in certain instances by examination of tissue by a pathologist who is familiar with examination of specimens of tissue obtained from bronchi.

Occasionally, more than one stenotic bronchus is found in the same patient. These may be found in the same lung, or one in each lung. We have similarly noted, in instances of recurrence of bronchostenosis, that stenosis may recur in the same bronchus, but that it may occur also in a different bronchus in the same lung, or it may occur in the opposite lung, and at bronchoscopy, moreover, the site of the original stenosis be found to be entirely clear. The prevention of recurrences of bronchostenosis apparently depends on the success the physician meets with in carrying out three procedures: first, avoidance of infections of the respiratory tract; second, postural drainage, and third, the treatment of the underlying causes of the patient's asthma. Almost every episode of bronchostenosis which complicates asthma may be traced to an acute infection of the upper or lower portion of the respiratory tract, chiefly the common cold. For the asthmatic person, a cold is many times an invitation to an episode of bronchostenosis. To avoid infections of the respiratory tract or "colds" (and thereby bronchostenosis), the patient should be advised (briefly): (1) to keep warm and dry, (2) to get plenty of rest and to avoid fatigue, (3) to avoid others who have colds, and (4) to take a stock catarrhal vaccine, this last being the least essential procedure of the group. Postural drainage is important in cases in which bronchial secretions are in excess. The physician should bear in mind the fact that in all instances in our series of cases bronchostenosis was always found in the lower half of the lung; in other words, the region to which excessive secretions gravitate. Postural drainage done at the patient's rising and before his retiring, or more often if necessary, will help to correct this stagnation of secretions that apparently contributes to the development of bronchostenosis. In many cases the raising of these secretions is materially aided by the administration of iodide preparations.

Bronchostenosis respects neither age nor sex. In our group the sexes were represented almost equally, 29 males and 31 females being affected.

cases on *Ferri sulfas* with 9.8 grams of hemoglobin at the onset of therapy and eight cases receiving *Ferri et ammonii citras* with an average initial blood hemoglobin of 10.1 gm. The chart shows the hemoglobin increase that resulted from this therapy in a 12-week period. While these are not as rapid as may be obtained with large amounts of iron, they represent a fairly satisfactory hemoglobin increase.

It is known that the same amount of iron is not equally effective in all patients so that a dose which is adequate in one may not be sufficient for another.<sup>28, 29</sup> Our results show, however, that a satisfactory hemoglobin response can be obtained in most instances with considerably smaller amounts of iron than are generally employed but they cannot be interpreted as indicating that large amounts are never advisable. The mechanism by which an excessive amount of iron produces a more rapid response than does an adequate amount has not been satisfactorily explained. Brock<sup>30</sup> has shown that "excess" iron is more effective than "enough" iron and Whipple<sup>31</sup> has asserted that the excess iron exerts a "salt" or catalytic effect. We have demonstrated that a larger amount of iron is retained with a greater intake and Moore<sup>21</sup> has shown that the serum iron rises higher with larger doses of an iron salt. Since hemoglobin is formed more rapidly when these large amounts of iron are available, even though only a small part of this available iron is utilized, it suggests that the rapid increase is due either to a greater ease of synthesis when excessive amounts of iron are present or that iron does not act entirely as a form of replacement therapy but has an additional stimulatory effect on hemoglobin formation. The results indicate, however, that it is not necessary to administer excessive amounts of iron in all cases of hypochromic anemia.

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ment of bronchostenosis which complicates asthma is dependent upon close coöperation between the internist and the bronchoscopist. If the internist fails to recognize the possibility of the presence of bronchostenosis in certain instances of asthma, and does not refer the patient for bronchoscopic examination, the true state of affairs will be entirely overlooked. If the bronchoscopist can examine these patients, the stenosed bronchus, if present, can be dilated and the retained secretions can be aspirated, with great benefit to the patient.

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## BRONCHOSTENOSIS COMPLICATING ALLERGIC AND INFECTIOUS ASTHMA \*

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BRONCHOSTENOSIS is a much more common complication of either allergic or infectious asthma than is generally believed. By bronchostenosis is meant a definite, localized, stricture-like narrowing of a bronchus. The lesion is felt to be primarily inflammatory in nature, and not referable to allergic edema or bronchial spasm. Two outstanding disturbances of function result when a bronchus becomes stenosed; first, the movement of air entering or leaving the segment of pulmonary tissue beyond the region of the stenosis is inhibited, and second, bronchial secretions which usually are excessive in asthma, are retained below the stenotic region so that a region of partial or complete atelectasis results.

During the past few years, a group of 140 patients suffering from asthma were specially selected for bronchoscopy, among whom we observed and treated 60 patients who were found to have definite stenosis of one or more bronchi. A study of this latter group revealed the fact that bronchostenosis complicating asthma generally produces characteristic symptoms and frequently, physical and roentgenologic observations which indicate that the physician may be dealing with this syndrome.

One of the more prominent symptoms encountered is severe, persistent, and sometimes paroxysmal cough, which of course aggravates the asthma. Frequently it is difficult or impossible, particularly at first, for the patient to raise sputum even by the most severe coughing. Later, the sputum appears, and it may become profuse. It is usually mucopurulent in character and in 40 per cent of the cases the sputum is at some time streaked with blood. The severe coughing is apparently caused by the patient's attempt to raise secretions retained by the stenotic region and later, when the stenosis recedes, either spontaneously or as a result of bronchoscopic dilatation, the retained secretions of a purulent or mucopurulent character are more easily raised. The source of the blood-tinged sputum is felt to be the seat of the bronchial inflammation and secondary pulmonary congestion which is present.

A second and very important symptom of bronchostenosis is fever. Febrile episodes, either with or without preceding chills, occurred in 68 per cent of the cases. The fever usually was of moderate severity and lasted from a few to many days. As the fever subsided, it was common for the patient to feel remarkably better and for the sputum to increase in amount.

\* Read before the meeting of the American College of Physicians, Cleveland, Ohio, April 5, 1940.

5. Electroencephalographic studies.
6. Therapeutic results.

1. *Sensitivity to Insulin.* From studies on experimental diabetes in animals and from clinical experience with diabetic patients, one knows that both men and animals may be hypo- or hyper-sensitive to insulin. Schizophrenic patients, like normal individuals and diabetics, also differ in their tolerance to insulin. Thus, in our experience the amounts of insulin which were necessary to provoke the so-called shock or hypoglycemic reactions varied from 25 to 400 units. Doses of 25 and 35 units consistently provoked profuse perspiration, very marked salivation and deep coma in three patients, 31, 60, and 46 years old; the duration of their illnesses was respectively, 6 months, 14 and 13 years. In contrast to the low tolerance for insulin in these three patients, a high tolerance was observed in two others, 16 and 17 years old, in whom the duration of their illnesses was respectively 17 and 18 months. In the 16-year-old patient not less than 200 units was necessary to provoke coma. In the 17-year-old patient, the dose which for a certain period consistently caused coma was 195 units. Then, smaller amounts, down to 100 units, had the same effect. This patient illustrates the fact that the tolerance to insulin may change considerably throughout the treatment.

2. *Reactions Following Individual Injections of Insulin.* The functions of both vegetative and somatic organs are more or less markedly disturbed following the administration of amounts of insulin high enough, according to the individual tolerance, to provoke untoward effects.

The most common reactions, under the control of the vegetative nervous system, are profuse perspiration and abundant salivation, the two reactions usually going on simultaneously. Some patients, however, while perspiring mildly or even remaining consistently dry, salivate considerably nevertheless and otherwise react intensively to insulin.

The cardiovascular system responds with marked fluctuations in the pulse rate. Bradycardia, with diminution of 20 to 30 beats, is usually first to occur; it is followed by return of the pulse rate to its original level, or by tachycardia—increases of 40 to 60 beats—in case the patient becomes restless. During coma, the pulse rate again fluctuates between levels below and above the starting point. Weakness and irregularity of the pulse are quite marked at times. Intermittent flushing of the face is of very frequent occurrence. Cyanosis of the face is observed in some patients inconsistently throughout the treatments. The blood pressure usually remains within physiological variations.

The respiratory system usually does not show significant changes in the precomatose phase of the treatment; the maximum fluctuation in the respiratory rate in one of our patients was from 18 to 28. In the comatose state, however, irregular, stertorous and deep heavy breathing are of frequent occurrence.

fuse the syndrome of bronchostenosis complicating asthma with true bronchiectasis. Kirklin<sup>1</sup> has described the roentgenologic picture of atelectasis, which is the most suggestive observation in bronchostenosis, as a "gauze-like shadow which extends more or less fan-like from the hilum toward the periphery of the lung and is of such slight density that the bronchovascular markings can be seen through it. Often an elevation of the corresponding arch of the diaphragm is associated with it and the heart and mediastinal structures may be displaced toward the affected side."

It should be emphasized that in 43 per cent of our cases results of the roentgenogram of the thorax were essentially negative. In still other cases, although the roentgenologic results were not negative, the roentgenologic observations were not significant in so far as the bronchostenosis was concerned. Several factors contribute to the high incidence of negative findings in roentgenograms in instances of bronchostenosis. In many instances the episode of bronchostenosis is not prolonged sufficiently to result in changes visible roentgenologically. In certain cases the opaque shadow cast by the heart obscures the affected portion as seen in the routine anteroposterior roentgenogram. In other instances in which long-standing previous bronchitis has been present, rather dense peribronchial shadows may obscure the more faint roentgenologic signs of atelectasis.

Only a relatively small group of patients who have asthma need bronchoscopy, and we feel the most common indication for such instrumentation is the need for ruling out or confirming the presence of possible complicating bronchostenosis. When the patient's history or the physical or the roentgenologic observations suggest the possibility of bronchostenosis which complicates asthma, such patients should have the benefit of a bronchoscopic examination, and should a stenotic bronchus be visualized, it can be dilated and the retained secretions can be removed by aspiration at the same time. It is common to see thick, tenacious mucus in excess in the bronchi, and often mucopurulent secretion is found. If stenosis of a bronchus is present at the time of bronchoscopy, a purulent secretion also may occasionally be seen oozing from the narrowed lumen of the bronchus. When the stricture is dilated by means of dilating forceps, varying amounts of retained mucopurulent or purulent secretion are found and may be aspirated. When patients who have asthma and a history suggesting bronchostenosis undergo bronchoscopy in the interval after they have apparently recovered from the complication, visualization of the bronchi may reveal no stenotic bronchus at the time, although in such cases there are usually increased secretions or other evidence usually encountered in instances of chronic asthmatic bronchitis. In other similar instances, some degree of stenosis persists, even after the febrile reaction has subsided, and its presence seems to aggravate the patient's cough and asthma and may contribute to frequent febrile episodes. Therefore, when a patient suffering from asthma who gives a history suggesting that he may have had complicating bronchostenosis in the past



The youngest patient was six years old, the eldest sixty-four. Seven patients were less than twenty years old; two were more than sixty. The intervening decades were represented by 10 to 15 cases each. Bronchostenosis may complicate asthma at any age.

The occurrence of allergy in our 60 cases was frequent and noteworthy. In half of the patients so affected the asthma had an allergic basis. Hay fever was experienced by ten individuals, and seven had a definite allergy to drugs. Other examples of allergy included vasomotor rhinitis, urticaria, angioneurotic edema, allergy to food and eczema. It should be emphasized again at this point that in the case of allergic asthma, just as in infectious asthma (asthmatic bronchitis), episodes of bronchostenosis were ushered in by intercurrent acute respiratory infections. Exposure to allergens did not bring about a single episode of bronchostenosis so far as we were able to determine.

The treatment of bronchostenosis, as has already been indicated, is achieved by dilatation of the stenosed bronchus by means of dilating forceps introduced through the bronchoscope. This procedure is immediately followed by aspiration of the retained secretions from the bronchus. The therapeutic instillation of preparations of radiopaque oil following aspiration has not added materially to the results obtained and has been largely discontinued. The immediate results, as measured by the relief of the patient, the subsidence of fever, the eventual reduction in amount and improvement in character of the sputum, the improvement in the course of the asthma, and in many cases, the immediate reversal of physical signs of bronchial obstruction, are excellent. As has already been stated, recurrences can and do ensue, but they can be prevented best by the patient's avoiding respiratory infections and his carrying out the other prophylactic measures already outlined.

Patients who have asthma are usually tolerant of careful bronchoscopy as done by an experienced bronchoscopist. It need hardly be mentioned that the sputum of all patients should be examined for tubercle bacilli before the examination, and the patients all should have had, previously, a complete general examination and in addition special examinations, such as an allergic survey, examinations of the nose and sinuses and roentgenologic studies of the thorax and sinuses. When an episode of bronchostenosis is obviously rather recent, and the fever is high, the acute process should be allowed to subside before bronchoscopy is carried out. Rarely do patients who have bronchostenosis object when bronchoscopy is advised; many patients sense the feeling that something unusual is interfering with their raising bronchial secretions which previously were relatively easy to raise, and are almost eager for the procedure to be done, and other patients have expressed wonder why no one had heretofore advised looking into their air passages to see if obstruction was present.

It is obvious, from the foregoing, that the recognition and correct treat-

semi-comatose state for nine more days. The body temperature gradually decreased and reached a normal level two weeks after the onset of coma.

The unexplained very prolonged coma and the other very serious complications had no therapeutic effect.

A 23-year-old male schizophrenic patient underwent a thorough physical examination—according to our usual procedure—before insulin therapy was instituted. No unusual findings were elicited.

From October 4 to October 25, 1938, the patient had 15 treatments. He reacted with coma in seven treatments with 65 to 90 units. During one treatment with 75 units he had a severe convulsion lasting 46 seconds. On October 25, the sixteenth day of the treatment, the patient was given 90 units at 7 a.m. At 9:20 a.m. myoclonic movements were noticed; they subsided by 9:30 a.m. At 9:45 a.m. the patient's pulse suddenly rose to 150 and a severe convulsion lasting 26 seconds followed. He was immediately given glucose by vein and nasal tube. At 10:08 he suddenly stopped breathing. Artificial respiration was instituted and adrenalin, caffeine, coramine and intravenous glucose were given. By 11:50 a.m. he was responding to questions and was groaning: "Oh, my God." At 1 p.m. he suddenly became more cyanotic. Artificial respiration and stimulants had no effect and by 1:25 he was pronounced dead. The post mortem by Dr. Langenstrass of St. Elizabeths Hospital revealed the following outstanding findings:

*Gross:* Acute dilatation of the heart. Extreme flaccidity of the myocardium and some turbidity.

*Microscopic:* Myocardium, liver, kidneys—intense, patchy congestion, areas of capillary stasis, swelling of parenchymal cells. Brain—moderate congestion, widely scattered, minute blood extravasations; one small leptomeningeal hemorrhage over cerebellum.

4. *Biochemical Studies.* In a previous study<sup>5</sup> 32 variables were analyzed in blood before the administration of insulin and during coma (table 1). Those variables marked with asterisks showed changes beyond normal

TABLE I  
Blood Constituents Studied in Insulin Therapy

1 Total protein	*11 Fermentable sugar	22 Cholesterol
2 Albumin	12 Sodium	23 Vitamin C (ascorbic acid)
3 Globulin	*13 Potassium	24 Hemoglobin
4 Non-protein nitrogen	14 Calcium	25 RBC count
*5 Urea nitrogen	15 Magnesium	26 Vol. pkd. RBC
6 Uric acid	*16 Serum solids	27 Mean corp. vol.
7 Creatinine	*17 Phosphorus (inorg.)	*28 WBC count
8 Total creatinine	18 Chlorides	*29 Differential count
*9 Amino acid nitrogen	19 CO <sub>2</sub> comb. power	30 Sedimentation test
*10 Sugar	20 CO <sub>2</sub> content	*31 Viscosity
	*21 Lactic acid	32 Clotting time

\* Constituents which showed changes during the insulin coma.

fluctuation and errors of the methods. Moreover, serum solids, potassium, phosphorus and sugar were analyzed in specimens of blood obtained at certain intervals following the administration of insulin (charts 2 and 3).

The main object of the present biochemical study is to supplement and at the same time test the accuracy of our previous findings by data obtained in another group of patients. Inasmuch as the results derived from this study

## PHARMACOLOGICAL TREATMENT IN SCHIZOPHRENIC PATIENTS \*

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THE insulin treatment of schizophrenic patients is essentially a medical treatment. Yet, it challenges the medical man, as well as the physiopathologist and the pharmacologist with respect to the generally accepted notions on the dosage of insulin compatible with safety, and with respect to the tolerance of various individuals to excessive amounts of this drug. The challenge lies chiefly in the fact that the complications of the insulin treatment—the so-called hypoglycemic shock—much dreaded by the physiopathologist—has been raised by the psychopathologist to a therapeutic virtue. Furthermore, the new treatment, aside from its curative value, in using the old drug in a new and very unorthodox manner, opens up a hitherto unexplored field for investigations. These promise to contribute not only to psychiatry and psychopathology but also, and perhaps more, to the chapters on general metabolism, and more specifically carbohydrate metabolism, and to our knowledge on the pharmacodynamics of insulin.

The insulin treatment of schizophrenia owes its origin to an accidental observation made by Sakel in his treatment of morphine addicts. First, he noticed that the insulin hypoglycemia had a calming effect on the motor restlessness of these patients. Then, in trying out the treatment in patients with varied psychotic conditions, he observed that in schizophrenic patients the quieting effect was most pronounced. While this observation was used by Sakel as the point of departure for the insulin shock treatment, he worked out a special therapeutic procedure to be used in schizophrenic patients.<sup>1</sup> Subsequently, the original method has undergone considerable modifications introduced by Sakel himself and by other investigators.<sup>2, 3, 4</sup>

The object of this paper is to record our experience with the following aspects of insulin shock therapy:

1. Sensitivity to insulin.
2. Reactions following individual injections of insulin.
3. Unusual reactions during and following termination of individual treatments. Hazards attached to the treatment.
4. Biochemical studies.

\* Read at the New Orleans meeting of The American College of Physicians, March 31, 1939.

From the Laboratories of St. Elizabeths Hospital, Washington, D. C., and Spring Grove State Hospital, Catonsville, Maryland.

We are indebted to the Supreme Council, 33° Scottish Rite Masons of the Northern Jurisdiction, U. S. A., for the financial help granted for our research work on schizophrenia.



TABLE II  
Blood Constituents Which Showed Changes During the Insulin Coma

	Cases No.	Tests No.	Decrease			Increase		
			Over 25%	10% to 25%	0% to 10%	0% to 10%	10% to 25%	Over 25%
Reduc. subst. ....	23	23	23 (25 to 90%)					
Ferment. sugar ....	16	16	16 (35.9 to 94%)					
Phosph. (inorg.) ....	39	46	14 (25 to 45%)	12	10	3	7	
Potassium ....	26	27	5 (25 to 45%)	13	8	1		
Amino acid N. ....	21	21	4 (26.9 to 34.4%)	11	3	2	1	
Urea nitrogen ....	9	9		5	4			
Viscosity ....	11	11			3	2	6	
Serum solids ....	20	22			1	15	6	
Lactic acid ....	8	12	1 (35%)			2	1	8 (25 to 239%)
WBC count ....	13	14						14 (50 to 368%)
Segm. neutro. ....	13	14				3	3	8 (25 to 77%)
Lymphocytes ....	13	14	12 (25 to 83%)	2				

proved to be similar to those of a former study,<sup>5</sup> we combined them in table 2. In addition we again examined serum solids, sugar (total reducing substances), fermentable sugar, inorganic phosphorus and amino-acid nitrogen in blood, before and at intervals of 1, 2, and 3 hours after the administration of insulin; the last or the last two specimens of blood were obtained during the comatose state. The study was done in 11 patients and 5 controls. The results obtained in each case are presented in three charts (4, 5 and 6).

*Comment.* A glance at the charts shows that the curves in the control studies are markedly different from the insulin curves. The serum solids were determined chiefly for the reason that in case of an apparent increase in the concentration of blood constituents the profuse perspiration very common in this treatment would raise the question whether the increase is wholly or partly due to increased specific gravity of blood. Notwithstanding the distinct tendency of the serum solids to increase, the other blood constituents show essentially a more or less marked but very definite decrease. The decrease is followed by a trend towards the original level; in some cases phosphorus rises above the starting level.

Sugar and fermentable sugar, as one would expect, considerably diminish and remain at a low level throughout the individual treatments. The simultaneous reduction in the blood content of sugar and inorganic phosphorus is of interest, since it was suggested that the insulin hypoglycemia might be due to the formation of some substance related to hexose phosphate. The curves of sugar and phosphorus do not keep pace, however, throughout, the former remaining low and the latter gradually rising to the original level and in some cases above that level.

The relationship between the hypoglycemia, the patient's reactions, and the dose of insulin is also worth noting: The kind and severity of the pa-

The body temperature more often than not goes down, and in some of our patients quite markedly. Thus, in one patient the rectal temperature dropped before the comatose phase in the course of several treatments from around  $99^{\circ}$  to  $97.8^{\circ}$  and  $94^{\circ}$ . Similarly, in another patient, the change of the temperature was from  $98.3^{\circ}$  to  $93.2^{\circ}$  in one treatment, and from  $97.4^{\circ}$  to  $91.6^{\circ}$  in another treatment. In contrast to these findings, an elevation of the axillary temperature from  $97^{\circ}$  to  $102.6^{\circ}$  was observed five hours after the termination of treatment, in a patient who was extremely restless and had generalized convulsions during the treatment. The physical examination was negative. The next morning the temperature was  $98.4^{\circ}$ .

The pupils remain either unaffected or dilated most of the time during the treatment; marked myosis occurs rather seldom. General muscular relaxation or rigidity is to be found frequently before the onset and during the comatose state. One patient, 28 years old, after the termination of a treatment with intravenous glucose could not grasp or hold objects with his right hand. This condition gradually cleared up within three hours. Tremor of the hands, and muscular twitchings particularly around the mouth, occasionally occur during the comatose state. In the precomatose phase, chills are of more frequent occurrence.

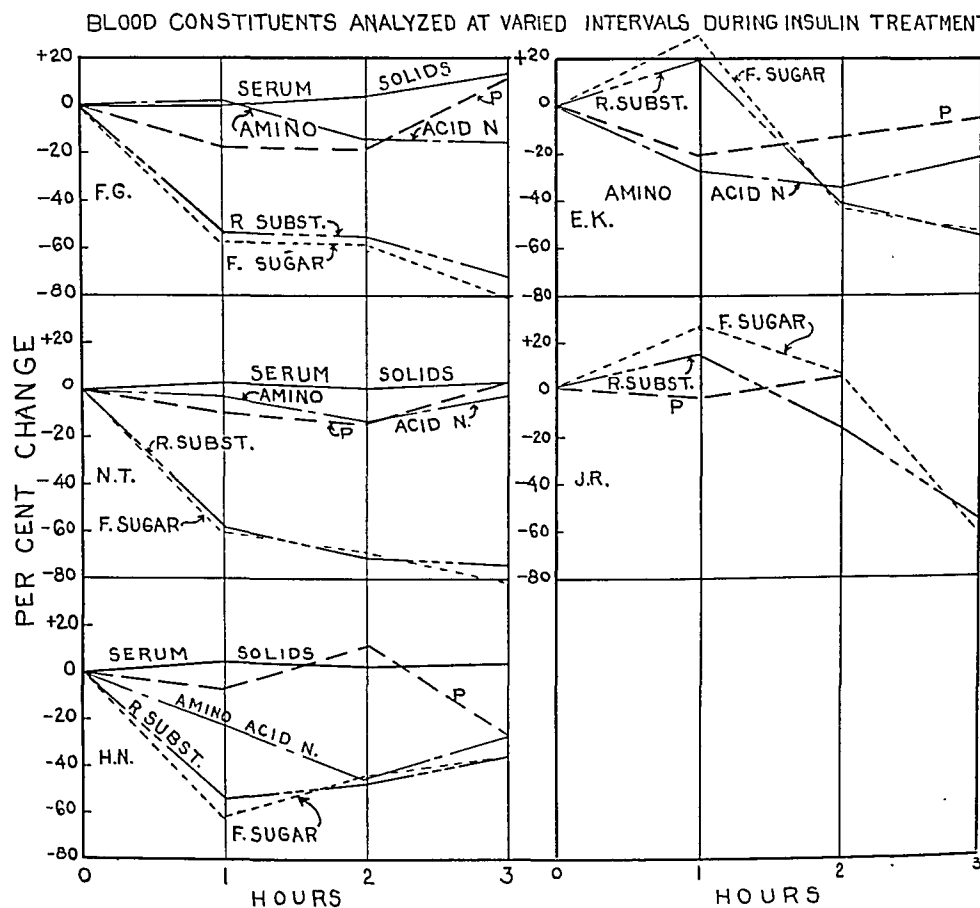
Abolition of the corneal reflexes, weakening of the plantar reflexes or a more or less marked extension of the big toe are quite common reactions during coma.

The most dramatic reactions and the ones which occur very frequently are excitement, motor restlessness, localized or more or less generalized clonic convulsions, and drowsiness, irrespective of whether or not the patient eventually goes into coma. In some patients muscular twitchings or frank convulsions originate either on the right side of the face or in the upper limbs or in both legs; they remain localized there, or culminate in generalized convulsions. Out of our 140 treated patients, 46 had convulsions during one or more individual treatments. While the proponents of the insulin treatment have changed their viewpoint in that they no longer regard convulsions as undesirable reactions, we found it beneficial, on certain occasions, to decrease their frequency or to reduce them to rather mild muscular twitchings with the help of sodium luminal; the hypnotic also offered the advantage of advancing the beginning of coma.

The reactions so far described usually occur in the following sequence: Perspiration and bradycardia become more or less pronounced within the first or second hour after the insulin injection. This is, usually, the phase of complete or relative calm; the quietness, however, is not infrequently disturbed by restlessness varying in intensity and duration and occurring also in patients who do not have convulsions. During the ultimate phase of, supposedly, supreme quietness (coma) localized or generalized convulsions may take place.

Each patient usually reacts to insulin along the same pattern throughout the treatments. Yet, the quality, intensity, sequence and duration of the

the first strip to each succeeding strip. In the two figures presented, the first strip in each figure corresponds to the earlier period of recording which was within two hours of the insulin injection. Chart 7 may be described as follows: A fairly normal alpha rhythm, 8-10 cycles per second predominated during the earlier interval of recording. This was followed by a gradual but steady decrease in the frequency of the brain waves as the hypoglycemia progressed. Within a few hours from the time of insulin injection a low frequency brain wave pattern averaging 3-cycles per second became frankly



predominant. It is interesting to note that these slow, relatively high voltage waves seemed to be independent of whether the eyelids were open or closed. Even a light flashed on the eyes gave rise to no distinct change in the brain wave pattern.

The other type of brain wave pattern (chart 8) was observed in 8 records. First, the frequency of the alpha wave pattern was around 10 cycles per second; this was followed by a 4 to 5 cycle per second rhythm. Then again, this slow wave pattern changed to a rhythm of about 10 cycles

reactions, all other conditions being equal, may vary not only in different patients but also in the same patient on different days. An illustration of the reactions as observed in the daily treatments during the whole period of the insulin therapy is presented in chart 1.

3. *Unusual Reactions During and Following Termination of Individual Treatments. Hazards Attached to the Treatment.* Eight out of 140 patients treated showed reactions deserving particular mention:

A female schizophrenic patient, 38 years old, received 110 units of insulin and was left in coma for one hour. She came out of coma, as usual, after the administration of glucose by nasal tube. Soon after lunch she had a generalized convulsion, followed by a cardiovascular collapse which rapidly yielded to adrenalin and intravenous glucose. Before glucose was given, the blood sugar was 122 mg. per 100 c.c. of blood. Within the next four hours, the patient had convulsions at intervals of about 20 minutes; in all there were 11 convulsive attacks. The last convulsion at 5 p.m. was followed by deep sleep, from which she awoke only the next morning, feeling well.

A female schizophrenic patient, 34 years old, was brought out of coma, as usual, with glucose given by tube. Fifteen minutes later her pulse became very weak, but it rapidly improved after the administration of adrenalin. Yet, the patient fell into coma (at about 1 p.m.) from which she came out only the next morning at 9 a.m. Within the first six hours of coma, the pulse was of good quality but rapid (120 to 140); the body temperature reached 103.2°; the blood sugar determined three times was 33, 47 and 53 mg. per 100 c.c. of blood in spite of many administrations of glucose by tube and vein. A spinal puncture done about five hours after the onset of coma had a calming effect on the patient's restlessness; the spinal fluid sugar was 143 mg. per 100 c.c. of blood. The patient's reaction to the treatments is also worth noting—when out of coma, she usually asked how many times she would have to die and added that she was happy at being again alive.

A female schizophrenic patient, 26 years old, on one occasion while her treatment was being terminated with intravenous glucose, stopped breathing. The apnea lasted three minutes yielding to artificial respiration and caffeine.

Three schizophrenic patients (one female and two males) throughout their treatment were usually brought out of coma by glucose given by tube after they remained in coma for 1 to 1½ hours. In each of them, in one treatment, the coma was unintentionally prolonged from 8 to 10 hours.

A white male patient reacted with coma to 115 units of insulin. No unusual reactions were noticed before and during the comatose state. In four successive treatments he was easily brought out from coma with the usual gavage of sugar. The next treatment with the same dose of insulin was marked by very unusual and very dramatic reactions. After the patient remained in coma for 1 hour and 15 minutes his pulse rate suddenly dropped from 130 to 76. He was immediately given glucose by nasal tube. Ten minutes later he showed slight cyanosis and a rather weak pulse. The cyanosis rapidly increased; the pulse became weaker and rapid; the respiration grew more and more labored and its rate rose to 60 per minute. Then the body temperature went up to 106° (F.) by rectum. Intravenous glucose, adrenalin, caffeine, coramine, and therapeutic doses of metrazol had no apparent effect. During the 48 hours following the onset of coma, it was necessary to give the patient considerable amounts of oxygen. After 24 hours of deep coma, the patient showed signs of improvement; the temperature dropped to 101.4°, and the respiratory rate went down from 60 to 36. Pulse and blood pressure showed no significant changes. The patient remained in a

# THE ANTICATALASE ACTIVITY OF SULFANILAMIDE AND SULFAPYRIDINE IN VIVO\*

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AN anticatalase activity of sulfanilamide in concentrations in vitro equivalent to those found in vivo during sulfanilamide therapy, was first observed by Main, Shinn and Mellon.<sup>13</sup> In extending these observations Locke, Main and Mellon<sup>11</sup> have concluded that hydrogen peroxide, which accumulates due to the diminished catalase activity, and not the sulfanilamide per se, is the active agent in combating bacterial infections. Hydrogen peroxide in pneumococcus cultures (Type 1, 18 hr. growth) was estimated by Shinn, Main and Mellon<sup>25</sup> who were able to detect concentrations as small as 0.0003 per cent. Retardation of growth of cultures containing sulfanilamide was accompanied by an increase in hydrogen peroxide as compared with the controls.<sup>14</sup>

Catalase is inactivated by hydroxylamine and chemically related compounds.<sup>2, 9</sup> Locke, Main and Mellon<sup>11</sup> claim that analogous anticatalase substances are produced from sulfanilamide when dilute solutions of the drug are exposed to ultraviolet irradiation. The anticatalase activity of the irradiated drug shows a marked increase with the development of the violet color which was first described by Ottenberg and Fox.<sup>13, 23</sup> This colored derivative of sulfanilamide (an oxidation product) forms a redox system which is present in the blood after sulfanilamide therapy (Fox, German and Janeway<sup>5</sup>). Mayer<sup>18</sup> found the para-hydroxylamine of benzenesulphonamide to be many times more active than sulfanilamide in vitro and in vivo. He believes this oxidized derivative of sulfanilamide to be the active agent formed in vivo.

Sulfanilamide produces unfavorable oxidation reduction potentials for the growth of hemolytic streptococci.<sup>5, 27</sup> Catalase lowers the electrode potential of a culture by decomposing hydrogen peroxide.<sup>7</sup> The facultative anaerobes, the streptococci and pneumococci are among the chief catalase producers and also are among the most active formers of peroxides.<sup>19, 20</sup> The addition of catalase to a culture of *Streptococcus hemolyticus* containing sulfanilamide reduces the bacteriostatic effectiveness of the drug. This is brought about by lowering the electrode potential, whereas sulfanilamide bacteriostasis is accompanied by an elevation in electrode potential, and normal growth by a rapidly falling potential.<sup>5</sup> The addition of 0.02 per cent hydrogen peroxide (in physiologic saline) to a culture of *Streptococcus hemolyticus* produces a lag phase in the growth of this organism in vitro, by

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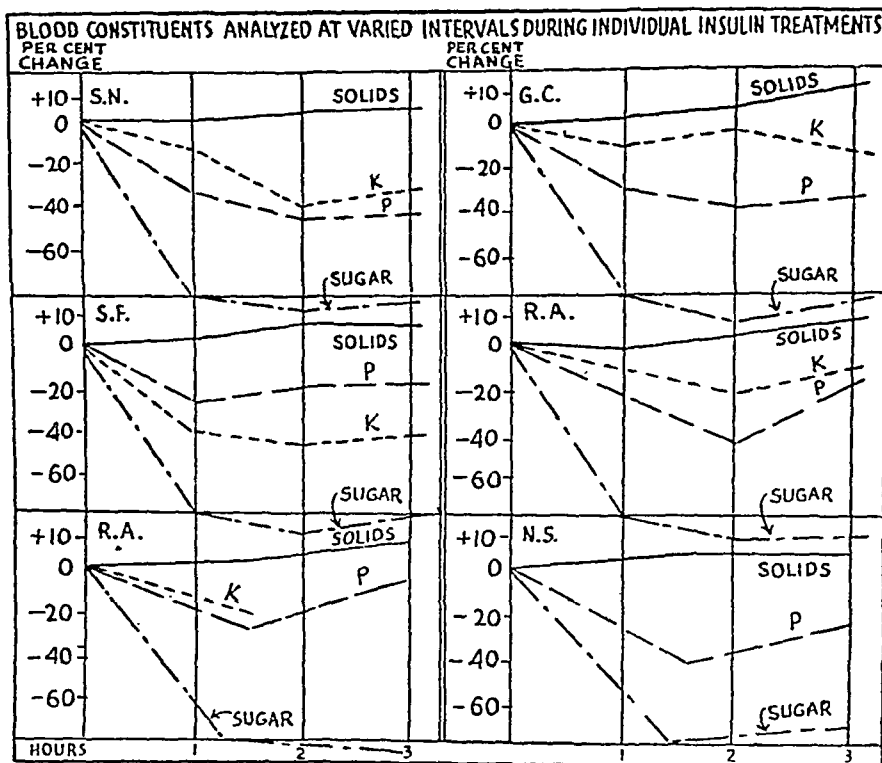


CHART II

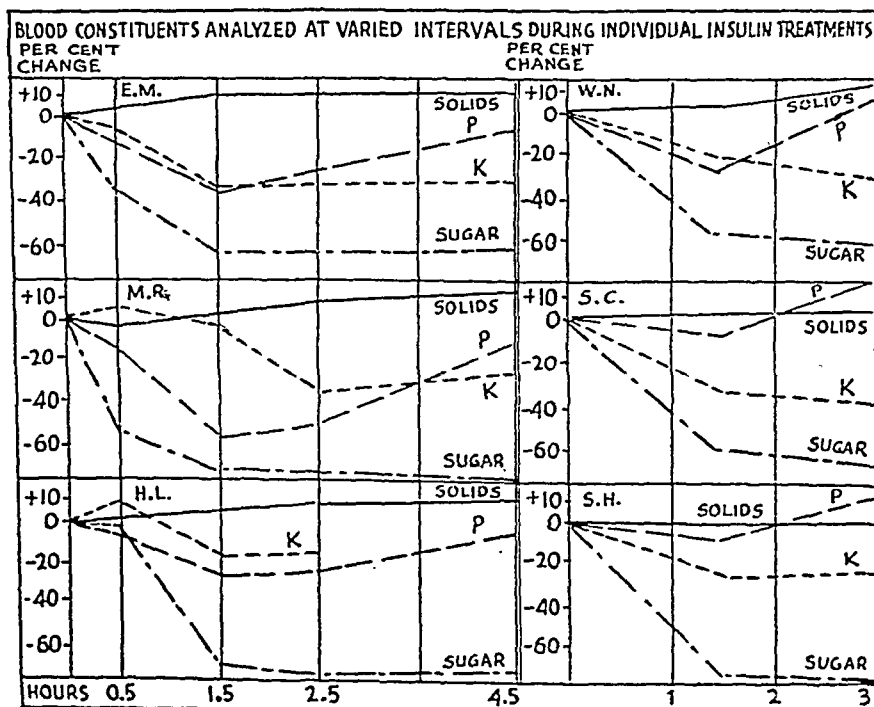


CHART III

Bach and Zubkova were 14 to 18 units (where the catalase value = mg. of hydrogen peroxide decomposed by 0.001 c.c. of blood and 1 unit = 1 mg. of hydrogen peroxide.) Values obtained by the writer on normal individuals, varying in age from 1 to 80 years, ranged from 16 to 20 units. The catalase values for each normal individual remained remarkably constant.

In animal experiments, nine rats (free of *Bartonella muris*) were employed. Five were treated with sulfanilamide; the remaining four served as controls. The rat was selected instead of the mouse because the excretion of sulfanilamide is slower and the drug can be maintained at the desired levels much more easily.<sup>17</sup>

The treated rats were given 0.4 gm. of sulfanilamide per kilo. per 24 hours in two doses of 0.2 gm. per kilo., at 9:30 a.m. and at 1:30 p.m. by subcutaneous route, using a 1 per cent solution of sulfanilamide (37.5° C.) in physiologic saline solution (sterile). The four controls received the same amount of saline in the same manner and at the same time. This was repeated for four successive days. Blood was taken from the tail at 5:00 p.m. Sodium oxalate was used as the anticoagulant; 0.02 c.c. was used for catalase determinations and 0.1 c.c. was used for sulfanilamide determinations where all reagents for the determination were proportionately reduced to 1/10. Centrifugation was used in place of filtration. All determinations were done in duplicate.

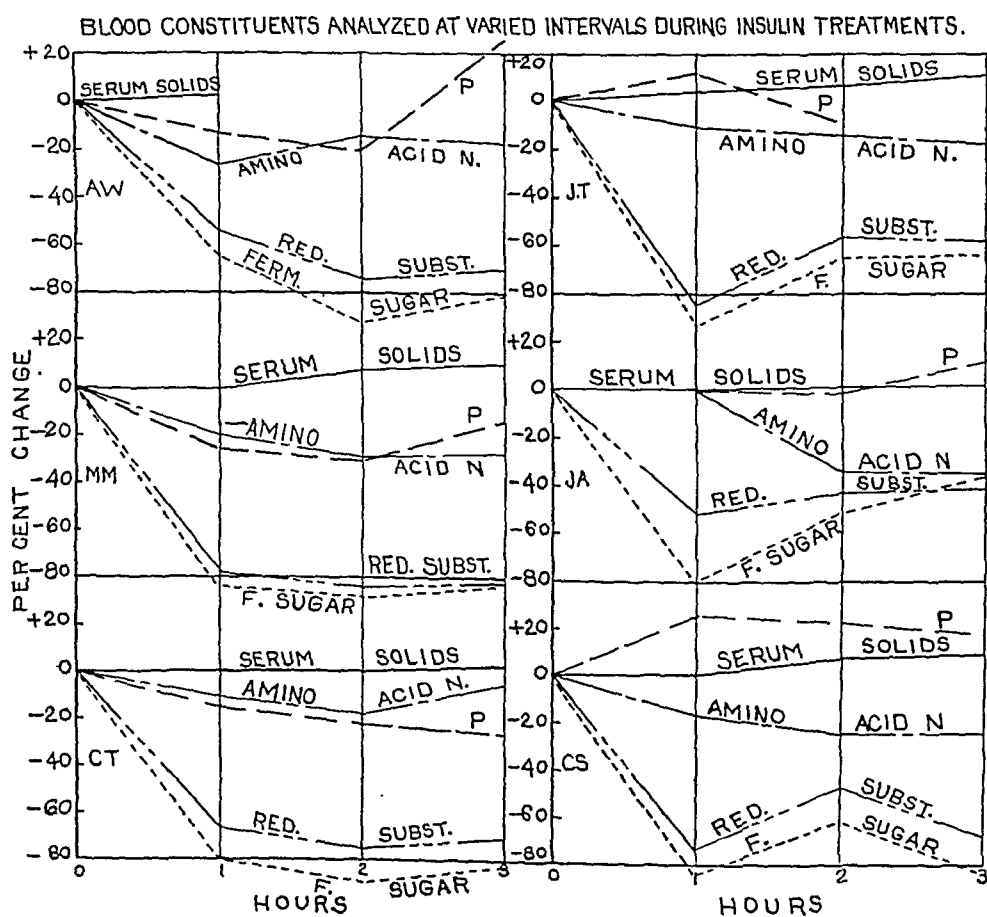
## RESULTS

All of the 15 patients except one showed a definite depression of the blood catalase activity. In contrast, the five controls showed practically no diminution of blood catalase activity. Eight of the treated patients showed a decrease of catalase activity of 20 per cent or more. The decrease occurred as soon as 12 to 24 hours after the administration of either sulfanilamide or sulfapyridine, reaching its lowest levels in 24 to 72 hours. Low levels of blood catalase values were obtained during the administration of the drug, the catalase activity usually returning to pretreatment levels after the drug was withheld, but in a more gradual manner. Although suggestive, no direct relationship could be established in these treated patients between the occurrence of minimum catalase values or persistence of low catalase values and the blood sulfanilamide or sulfapyridine levels. This can be seen by referring to table 1. Patient 1 shows a 47 per cent decrease in catalase activity with an 8 mg. per cent sulfapyridine blood level, and patient 12 a decrease of 44 per cent, with a blood level of sulfanilamide of 1 to 3 mg. per cent. This is in contrast to patient 7 who shows a 17 per cent decrease in catalase activity with a sulfapyridine blood level of 16 mg. per cent. Shinn, Main and Mellon<sup>25</sup> found, in studies of anticatalase activity of sulfanilamide made in vitro, a maximum suppression of catalase activity in 2 mg. per cent solutions of sulfanilamide. One patient, number 10, responded to sulfanilamide with a rise in blood catalase activity. This was a mild case

tient's reactions, the degree of the hypoglycemia and the dose of insulin are not consistent in their relationships—either qualitative or quantitative ones—in different patients and in the same patient in different individual treatments.

5. *Electroencephalographic Studies.* Brain action potentials were studied in 17 schizophrenic patients under the insulin treatment.

The apparatus used consisted of a single channel push-pull condenser-coupled amplifier and ink writing oscillograph constructed in our own laboratory (by Dr. Robert Cohn), according to the design introduced by Davis



and Grass. The linear frequency response of this apparatus, within 1 mm., is from 2.5 to 25 cycles per second. The discharge time (time constant) is 0.2 second. Electrodes were uniformly placed over the midfrontal and midoccipital regions of the head.

From a total of 50 records, two quite distinct types of "brain waves" were noted:

The one type observed in 42 records is seen in chart 7. The time, in minutes, noted under each strip of record indicates the time elapsed from



TABLE I—*Continued*

Case No.	Age Yrs.	Sex	Diagnosis	Date (1939)	Treatment	Total Amount of Drug Grams	Blood Level of Drug Mg. %	Catalase Units
9	44	M.	Lobar pneumonia	Feb. 10	Before	20	0	16.5
				Feb. 11	Sulfapyridine		12	13.7
				Feb. 13	Sulfapyridine		15.5	12.7
10	4	M.	<i>Streptococcus hemolyticus</i> pharyngitis	Feb. 15	After	7	2	18.2
				Feb. 11	Before		0	16.5
				Feb. 12	Sulfanilamide		4	16.5
				Feb. 13	Sulfanilamide		3.5	17.2
				Feb. 15	After		2	18.5
				Feb. 18	After		0	19.2
11	58	M.	Lobar pneumonia	Feb. 21	After	24	0	20.6
				Feb. 13	Before		0	18.9
				Feb. 15	Sulfapyridine		9.8	16.1
				Feb. 16	Sulfapyridine		8	16.4
				Feb. 18	After		7	18.2
				Feb. 20	After		2	18.2
12	6	M.	Otitis media	Feb. 16	Before	10	0	23.1
				Feb. 17	Sulfanilamide		3	13.6
				Feb. 18	Sulfanilamide		1	12.9
				Feb. 20	Sulfanilamide		0.8	19.9
				Feb. 21	After		Trace	18.2
				Feb. 22	After		0	18.9
13	12	M.	Lobar pneumonia	Feb. 13	Before	20	0	18.2
				Feb. 15	Sulfapyridine		4.6	16.1
				Feb. 16	Sulfapyridine		5	15.0
				Feb. 19	After		0	18.2
				Feb. 21	After		0	19.9
				Feb. 16	Before		0	16.8
14	46	M.	Lobar pneumonia	Feb. 17	Sulfapyridine	25	8	16.1
				Feb. 18	Sulfapyridine		9	14.3
				Feb. 20	Sulfapyridine		3	17.5
				Feb. 21	Sulfapyridine		Trace	17.8
				Feb. 11	Before		0	16.1
				Feb. 12	Sulfanilamide		6.5	16.7
15	2	M.	Naso-pharyngitis	Feb. 13	Sulfanilamide	7	4.8	15.4
				Feb. 14	After		1.5	16.1
				Feb. 15	After		Trace	16.1
				Apr. 27	Before			23.4
				Apr. 27	200,000 units			23.4
				Apr. 28	Type I anti-pneumo. serum			23.4
16	46	M.	Lobar pneumonia type I	Apr. 29	After			20.9
				May 1	After			18.7
				May 3	After			20.4
				May 4	After			21.7
				May 5	After			22.4

The five control cases showed negligible variations in blood catalase values.

Two patients in this series died. Case 11, a patient suffering from lobar pneumonia, treated with sulfapyridine, showed only a 16 per cent maximum diminution of catalase activity with a blood level of 9.8 mg. per cent sulfapyridine. The other, case 3, received neither drug and showed a slight elevation of blood catalase activity. This patient was in the hospital for only three days.

per second. These fluctuations took place quite irregularly, usually 2 to 5 times during the entire recording.

In both types of brain wave patterns during most of the slow wave stage the patient appeared to be in deep coma. The eye reflexes were usually absent; the breathing was deep, regular and noisy; no response to auditory or tactile stimuli could be elicited. During some of the alpha wave stage of

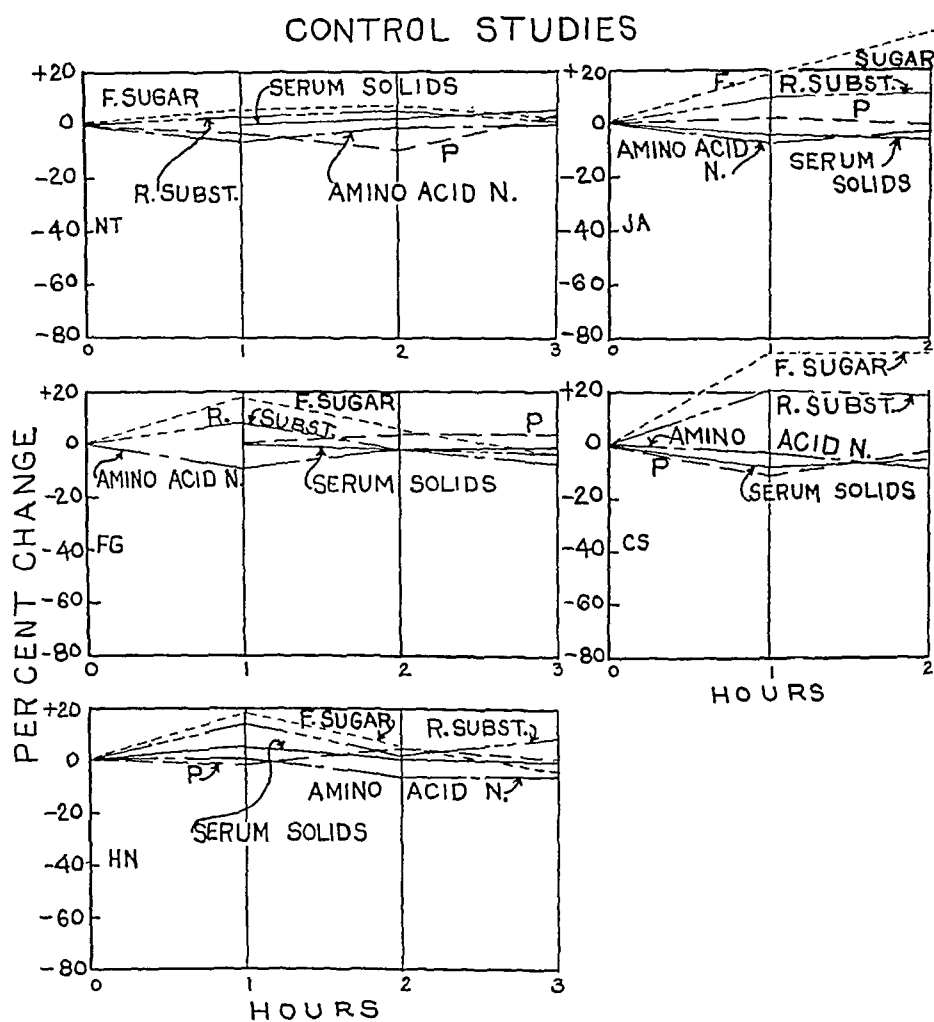


CHART VI

the second type of brain wave pattern these individuals seemed alert, and in at least two instances the subject was more lucid and accessible than usual.

There was a striking parallelism between the variations in the brain potentials and the changes in the blood sugar content. Thus, with intravenous glucose the return of the brain wave pattern to the original preinsulin type was quite rapid—often within ten minutes; with gavage the return to the original pattern was usually longer, but not exceeding 30 minutes after the administration of glucose.

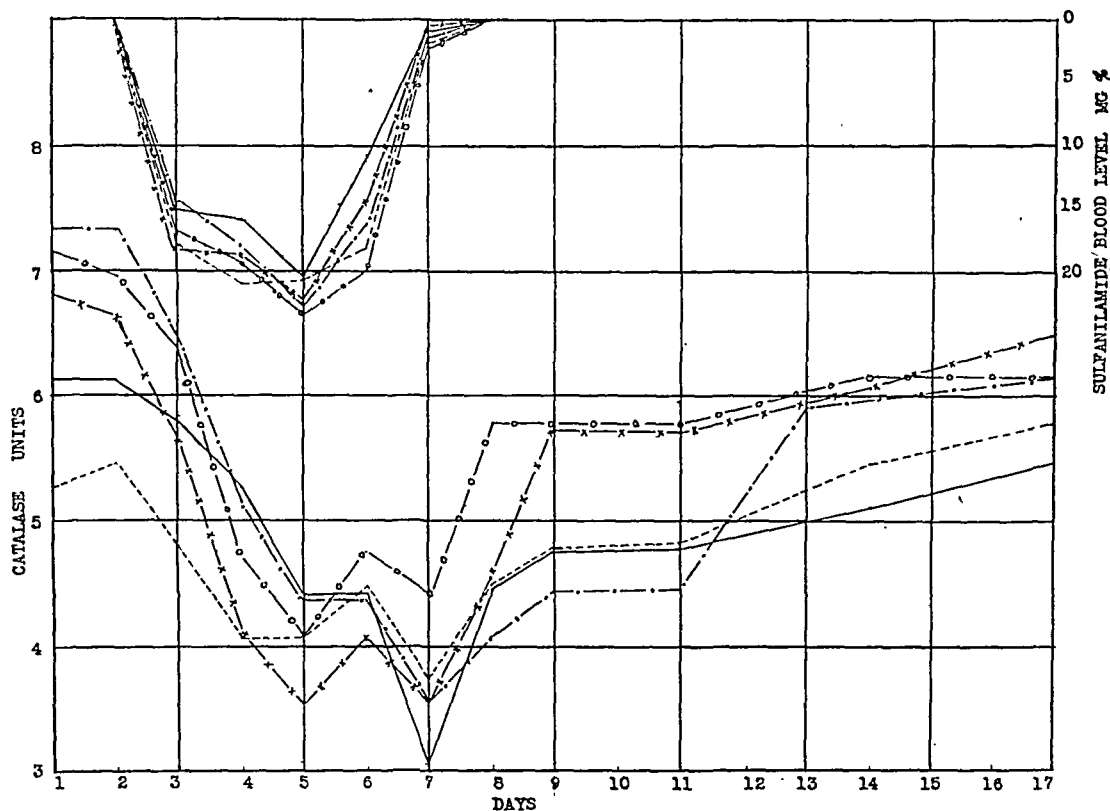


FIG. 1. Sulfanilamide treated rats.

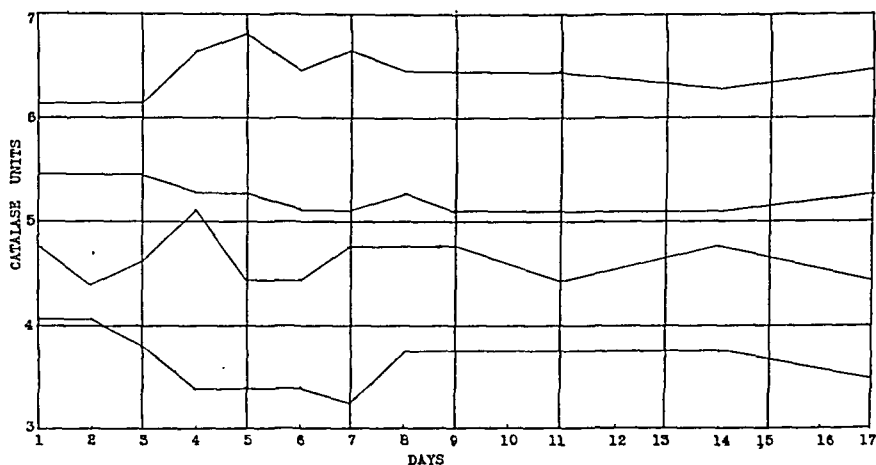


FIG. 2. Control rats.

controlled conditions of the rat experiments. The average maximum decrease of the catalase activity in the treated rats was 45.6 per cent.

#### COMMENT

From the above results it is evident that sulfanilamide and sulfapyridine decrease the blood catalase activity in man and rats. This demonstrates a

elevating the electrode potential.<sup>5, 6, 8</sup> Sulfapyridine affects the electrode potential in the same manner.<sup>27</sup>

The enzyme catalase has recently been isolated in crystalline form by Sumner and Dounce<sup>26</sup> and is shown to be an iron porphyrin compound. Bacteria devoid of iron porphyrin compounds live by an anaerobic fermentation process. The streptococci and pneumococci are facultative anaerobes, and sulfanilamide does not act on these organisms if air is excluded from the cultures.<sup>5, 27</sup> Thus under anaerobic conditions these organisms continue to grow in the presence of sulfanilamide. This phenomenon may be explained in three ways: (1) peroxide is formed in aerated cultures of hemolytic streptococci, and not under anaerobic conditions<sup>6</sup>; (2) in complete absence of molecular oxygen the activity of catalase is completely abolished<sup>10</sup>; (3) the electrode potential is lowered in sterile broth in the absence of oxygen<sup>3, 4</sup> and is further lowered in the presence of hemolytic streptococci.<sup>6</sup> This absent activity of sulfanilamide under anaerobic conditions occurs *in vivo* as well as *in vitro*.<sup>12</sup> McLeod and Gordon<sup>19</sup> found that anaerobes that do not produce catalase are particularly susceptible to hydrogen peroxide.

With the available evidence of the influence of catalase on bacterial growth and the anticatalase effect of sulfanilamide *in vitro*, it appeared desirable to investigate quantitative changes in catalase in patients and animals receiving sulfanilamide or sulfapyridine.

## METHODS

Blood catalase determinations were done on 21 patients. Fifteen subjects were receiving sulfanilamide or sulfapyridine, one patient was receiving antipneumococcal serum, and five received neither sulfanilamide, sulfapyridine nor serum. Since in studying the *in vitro* anticatalase effect of sulfanilamide Shinn, Main and Mellon<sup>25</sup> had employed cultures of pneumococci, nine proved cases of lobar pneumonia (pneumococcus) were included among the 15 cases selected for treatment. Samples of oxalated blood obtained by venipuncture were examined quantitatively for catalase before, during and after the administration of sulfanilamide or sulfapyridine, the blood levels of the drugs used being determined simultaneously. Striking changes were observed. The results obtained in man were confirmed under controlled experimental conditions in rats.

The catalase determinations were done by the method of Bach and Zubkova,<sup>1</sup> modified by using Sorensen's phosphate buffer (pH 6.8) instead of distilled water in the reaction mixture. This was done because of the work of Morgulis<sup>21</sup> who found that in the presence of sufficient buffering, the catalase reaction becomes directly proportional to the concentration of the enzyme, and independent of the hydrogen peroxide concentration, the optimum pH being 6.8 with an active range of 6.5 to 8.5. The determinations of sulfanilamide and sulfapyridine blood levels were done by the method of Marshall and Litchfield.<sup>16</sup> The normal range of catalase values obtained by

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of pharyngitis in a four year old negro, who was not acutely ill, but who responded well to treatment clinically with sulfanilamide. A maximum blood level of 4 mg. per cent was obtained.

No definite correlation could be established between the maximum percentage suppression of blood catalase activity, the dose of the drug given and the number of days treatment. Again referring to case 1, 22.5 gm. sulfapyridine given over a period of six days resulted in a 47 per cent diminution of blood catalase activity; and in case 8, 15 gm. given over four days resulted in a 40 per cent diminution of blood catalase activity.

TABLE I  
Patients Receiving Sulfanilamide, Sulfapyridine, or Serum

Case No.	Age Yrs.	Sex	Diagnosis	Date (1939)	Treatment	Total Amount of Drug Grams	Blood Level of Drug Mg. %	Catalase Units
1	10	M.	Lobar pneumonia	Feb. 1	Before	22.5	0	18.2
				Feb. 1	Sulfapyridine		7	14.7
				Feb. 3	Sulfapyridine		8	12.9
				Feb. 6	Sulfapyridine		9	16.8
				Feb. 11	After		3	9.6
				Feb. 11	After		Trace	19.1
2	15	F.	Lobar pneumonia	Feb. 6	Before	12.5	0	12.9
				Feb. 8	Sulfapyridine		8	11.0
				Feb. 10	Sulfapyridine		12	15.2
				Feb. 13	After		Trace	11.0
				Feb. 15	After		0	14.0
				Feb. 6	Before		0	18.2
3	27	M.	Lobar pneumonia	Feb. 9	Sulfapyridine	32	8	14.0
				Feb. 11	Sulfapyridine		12	14.7
				Feb. 13	After		1.4	14.1
				Feb. 15	After		Trace	18.2
				Feb. 10	Before		0	17.2
				Feb. 13	Sulfanilamide		3	13.4
4	2	M.	Bilateral otitis media	Feb. 15	Sulfanilamide	16	1.3	14.7
				Feb. 18	Sulfanilamide		1.8	16.8
				Feb. 19	After		Trace	17.2
				Feb. 21	After		0	18.2
				Feb. 9	Before		0	17.2
				Feb. 10	Sulfanilamide		7	15.2
5	1.5	M.	Acute pharyngitis	Feb. 13	Sulfanilamide	10	9	12.4
				Feb. 15	After		1.8	15.4
				Feb. 16	After		Trace	16.8
				Feb. 9	Before		0	15.9
				Feb. 11	Sulfapyridine		6	14.3
				Feb. 13	Sulfapyridine		8	12.7
6	3	M.	Lobar pneumonia	Feb. 15	After	11	1.4	12.9
				Feb. 18	After		Trace	14.4
				Feb. 20	After		0	16.1
				Feb. 22	After		0	16.4
				Feb. 9	Before		0	15.9
				Feb. 11	Sulfapyridine		16	13.3
7	55	M.	Lobar pneumonia	Feb. 13	Sulfapyridine	20	14	16.2
				Feb. 15	After		4	15.0
				Feb. 16	After		1	16.2
				Feb. 11	Before		0	18.2
				Feb. 13	Sulfapyridine		12	11.0
				Feb. 15	Sulfapyridine		19	13.6
8	9	M.	Rheumatic fever	Feb. 18	After	15	2	16.1
				Feb. 20	After		0	17.3

minute. The student resumed his sitting position in the comfortable chair and his arm placed upon a table of convenient height. The blood pressure and pulse rate were taken at each  $\frac{1}{2}$  minute interval for 2 minutes, then each successive minute until the systolic and diastolic pressures and the pulse rate returned to the basal level. The 96 hypertensive, 56 hypotensive and 128 normal subjects on which the cold pressor test had been conducted for vaso-motor response were used to study the comparative effect of exercise on the three groups.

The systolic blood pressure of 20 per cent of the hypertensive cases increased over 60 mm. Hg. In 2 per cent the increase was over 80 mm. Hg (table 1). The systolic pressure in the normal group failed to increase

TABLE I  
Comparison of Blood Pressure Response to Exercise

Blood Pressure	Mm. Hg increase in systolic pressure above basal level Mm. Hg decrease in diastolic pressure below basal level										
	0	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	over	Aver.
<i>High</i>											
Systolic . . .			2.1 *	18.7	10.4	27.1	20.8	12.5	6.2	2.1	48
Total† . . .			2.1	20.8	31.2	58.3	79.1	91.6	97.8	99.9	
Diastolic . . .	10.4	43.7	25.0	18.7	0	0	2.1				15
Total . . .	10.4	54.1	79.1	97.8			99.9				
<i>Normal</i>											
Systolic . . .			20.0	17.1	25.7	19.9	17.2				37
Total . . .			20.0	37.1	62.8	82.7	99.9				
Diastolic . . .	5.7	42.8	42.8	8.5							12
Total . . .	5.7	48.5	91.3	99.8							
<i>Low</i>											
Systolic . . .		8.3	25.0	58.3	8.3						23
Total . . .		8.3	33.3	91.6	99.9						
Diastolic . . .	8.3	33.3	50.0	8.3							13
Total . . .	8.3	41.6	91.6	99.9							

\* All figures expressed in per cent of cases studied, except last vertical column which is expressed in mm. Hg, average increase in systolic and average decrease in diastolic blood pressure.

† Represents accumulative total per cent of students for each subsequent 10 mm. change in blood pressure.

more than 50 mm. in 82.7 per cent of the cases and in none did it rise more than 60 mm. In the low blood pressure group, 91.6 per cent of the subjects failed to show an increase of more than 30 mm. and in none did the pressure increase more than 40 mm. The average increase of the systolic pressure was 48, 37, and 23 mm. Hg for the hypertensive, normal and hypotensive classes, respectively. The diastolic pressure in all three groups decreased, as shown in table 1. Over 91 per cent of the cases in the normal and hypotensive classes and 79 per cent of the hypertensive subjects did not have more than a 10 to 20 mm. decrease in the diastolic pressure. Only

TABLE II  
Control Patients

Case No.	Age Yrs.	Sex	Diagnosis	Date (1939)	Catalase Units
1	34	F.	Lobar pneumonia	Feb. 18	16.8
				Feb. 20	16.1
				Feb. 21	16.4
				Feb. 23	17.2
				Feb. 25	17.5
2	16	M.	Lobar pneumonia	Feb. 26	17.5
				Feb. 19	18.2
				Feb. 20	18.5
				Feb. 21	17.8
				Feb. 23	18.2
3	54	F.	Lobar pneumonia	Feb. 25	17.8
				Feb. 10	14.7
				Feb. 12	15.4
4	9	F.	Broncho-pneumonia	Feb. 13	15.3
				Feb. 16	15.1
				Feb. 18	14.7
				Feb. 19	14.3
				Feb. 21	15.1
5	6	M.	Lobar pneumonia	Feb. 23	14.7
				Feb. 15	16.8
				Feb. 17	16.2
				Feb. 18	17.2
				Feb. 20	17.5
				Feb. 22	17.8

The clinical course of the patients treated with sulfanilamide or sulfa-pyridine usually paralleled the drop in catalase activity. The temperature, pulse and respirations fell and other symptoms subsided as the catalase activity dropped.

Case 16, a patient with Type 1 pneumococcal lobar pneumonia, received 200,000 units of antipneumococcus serum within two days. It is noteworthy that this patient showed a fall in blood catalase activity three days after the serum treatment was begun, reaching a maximum decrease of 21 per cent on the fourth day after treatment was initiated.

*Observations Made on Rats.* Rats receiving sulfanilamide showed an immediate drop in blood catalase values simultaneously with the administration of sulfanilamide. The maximum diminution occurred 24 hours after sulfanilamide was discontinued. Blood sulfanilamide in these rats reached a maximum of 20 to 23 mg. per cent, and the rise in blood concentration showed a definite time relationship to the low blood catalase values (figure 1). The return of blood catalase values to their previous normal levels was gradual. This sequence is similar to that observed in man.

Rats serving as controls showed only slight and variable changes in catalase values, in contrast to the marked lowering of the blood catalase value of the sulfanilamide treated rats (figure 2). The effect of sulfanilamide in its anticatalase action is more evident and uniform in the treated rats than in the treated patients. This can probably be explained by the



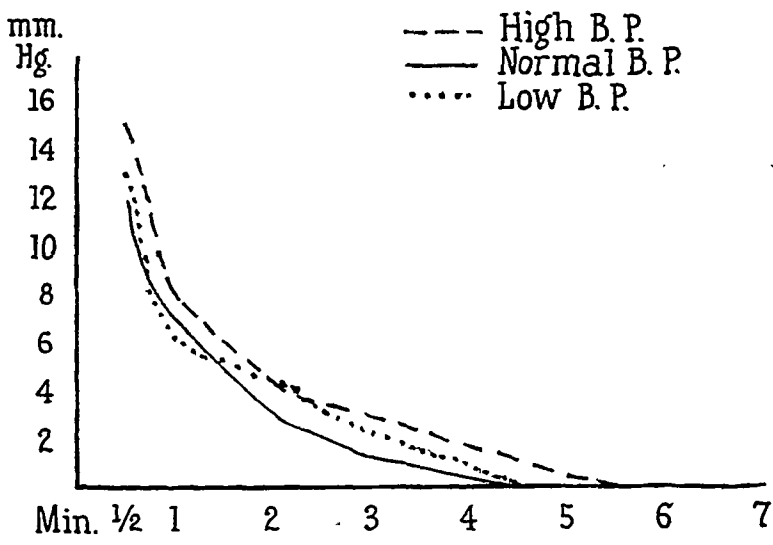
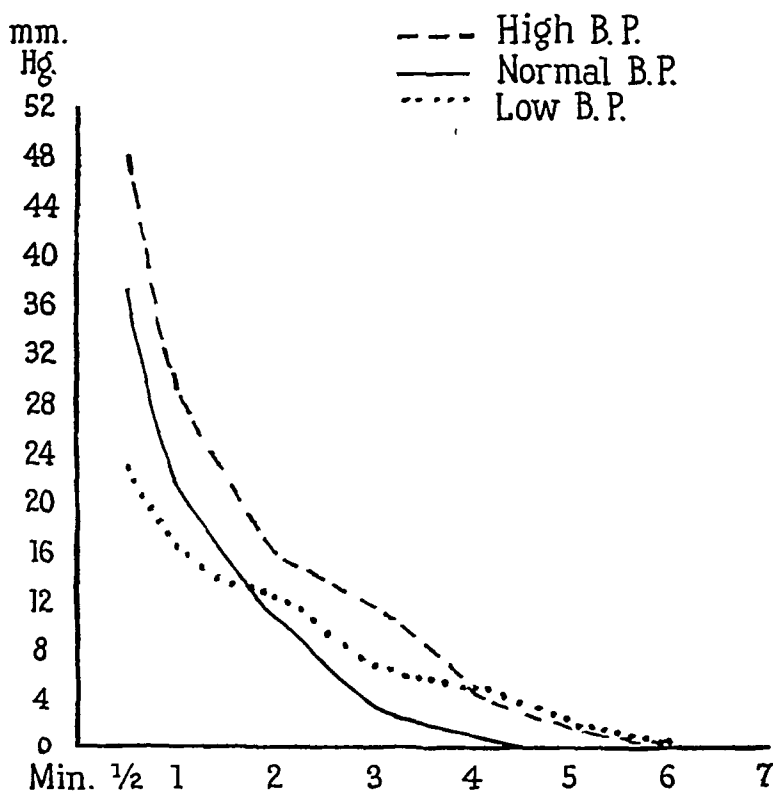


FIG. 1. Comparison of the average systolic blood pressure following exercise, showing the amount of increase and the time to return to the basal level.

FIG. 2. Comparison of the average diastolic blood pressure following exercise, showing the amount of decrease and the time to return to the basal level.

change in living organisms similar to in vitro observations. Although blood catalase activity is affected to a greater extent in rats, the changes in man are sufficient to permit the postulation of significant effects.

That the mode of action of sulfanilamide postulated by Locke, Main, and Mellon<sup>11</sup> on the basis of experiments with pneumococcus cultures can be extended to describe its action in higher animals is shown in this paper.

Thus there occurs reduction of catalase activity (and probably alterations of other enzymic systems) either by these drugs, or more likely by an oxidation product of these drugs, to levels that allow an accumulation of hydrogen peroxide in the area of infection in concentrations sufficient to raise the electrode potential of the tissues of the host. In this manner conditions are made temporarily unfavorable for normal oxidation-reduction processes of the invading organisms. The resultant bacteriostasis then enables the tissues of the host to eliminate dormant, non-metabolizing organisms by the activity of the phagocytic mechanism in the area of infection.

### SUMMARY

1. A definite diminution of the blood catalase activity in 14 of 15 patients treated with sulfanilamide or sulfapyridine has been demonstrated. A similar response has been shown to occur in rats.

2. A possible mode of action of sulfanilamide based on the anticatalase effect in vivo is described.

I wish to express my thanks to the chiefs of the Medical and Pediatric Departments for permission to study their patients, to Dr. J. H. Clark for the use of the laboratory facilities and to Drs. J. G. Reinhold and S. B. Rose for advice and criticism during the course of experimentation.

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Table 4 gives a summarized average tabulation of the blood pressure observations, including the results of the cold pressor test. The diastolic pressure following exercise in each group fell about the same amount below the basal diastolic pressure level as it increased above this level with the cold pressor test. The maximum average systolic pressure after exercise in the hypertensive group rose 30 mm. above the ceiling reached when the cold test was used. The regular or usual systolic blood pressure in the hypertensive class was 28 mm. above the basal level as compared to 5 and 7 mm. in the low and normal groups.

TABLE V  
History Findings for Subjects Observed in Blood Pressure Study

	H. B. P.*	N. B. P.*	L. B. P.*
<i>Emotions</i>			
Nervous and Excitable.....	43.7	11.7	14.3
Stable.....	54.0	56.3	85.7
H. B. P. in family.....	54.1	3.1	5.3
L. B. P. in family.....	0	2.3	17.8
<i>Exercise</i>			
Vigorous.....	6.2	6.2	7.1
Moderate.....	40.6	35.1	50.0
Mild.....	51.0	58.5	42.8
<i>Quantity of food eaten</i>			
Heavy eater.....	35.4	14.8	14.3
Medium eater.....	63.5	78.9	78.5
Light eater.....	1.1	6.2	7.1
<i>Simulants</i>			
Coffee.....	12.5	11.7	28.5
Tobacco.....	16.6	19.5	50.0

\* Indicates high blood pressure, normal blood pressure and low blood pressure, respectively. Figures in each vertical column represent the per cent of cases studied.

Some interesting information was obtained from the detailed history of these students (table 5). It was noted that 11.7 per cent of the normal, 14.3 per cent of the low pressure group, and 43.7 per cent of the hypertensive class presented evidence of being nervous or easily excited. Furthermore, 3.1 per cent of the normal and 5.3 per cent of the low blood pressure subjects and 54.1 per cent of the hypertensive group gave a history of familial hypertensive cardiovascular disease. The information obtained revealed that 17.8 per cent of the hypotensive class gave a family history of low blood pressure, whereas, none of the high blood pressure group and only 2.3 per cent of the normal subjects indicated any such disturbance among members of their immediate family or preceding generation. In the series of cases observed by Hines and Brown,<sup>3</sup> five times as many patients who had high blood pressure gave a positive family history of hypertensive cardiovascular disease as did subjects with normal blood pressure. This investigation not only confirms their results, but also indicates that there is a marked tendency for essential hypotension to be familial. There appears to be a definite hereditary pattern for blood pressure reaction. Perhaps this depends for the most part

# BLOOD PRESSURE STUDIES ON UNIVERSITY STUDENTS, INCLUDING THE EFFECT OF EXERCISE ON ESSENTIAL HYPERTENSION, HYPOTENSION, AND NORMAL SUBJECTS \*

By E. A. THACKER, M.S., M.D., *New Orleans, Louisiana*

It is evident from the accumulation of articles in the scientific literature, that many factors influence the level of blood pressure. However, with our present knowledge, the cause of essential high and low blood pressures remains quite obscure.

The purpose of this investigation has been to study the normal and abnormal blood pressures among university students and to ascertain the effect of exercise upon them from a comparative standpoint. A history and physical examination are obtained on each entering student. This study included the observation of 15,500 male students at the University of Illinois from 1935 to 1939. Those with high and low blood pressure and a normal control group were rechecked at intervals. Detailed information was obtained on factors which might have an effect on the blood pressure, such as illnesses, habits, diet, family history, etc.

The students with a systolic blood pressure over 150 mm. Hg at the time of their entrance physical examination were put into the hypertension group. All students with a systolic pressure upon entrance below 108 were classified in the hypotension group. The control group consisted of matriculants with systolic pressure between 114 and 138 mm. Hg. The exercise test was not done on discernible cases of organic heart, kidney or thyroid disease.

A variation of the cold pressor test, as described by Hines and Brown <sup>1</sup> was done on these students. As reported elsewhere, <sup>2</sup> this portion of the investigation revealed: (1) The hypertensive and hypotensive classes were slower in reaching their maximum increase in the systolic and diastolic pressures; (2) there was a greater increase in the systolic and diastolic blood pressure of the hypertensive subjects than of the control group; (3) the high and low blood pressure groups returned to their basal level more slowly than did the normal subjects.

## BLOOD PRESSURE RESPONSE TO EXERCISE

The basal blood pressure and pulse were obtained by having the student rest for a 30 minute period, or until repeated blood pressure readings and the pulse rate remained at a constant basal level. All cases performed the same type of exercise, which consisted of raising the weight of the body 20 times from the floor on to a chair 18½ inches high at the rate of 40 cycles per

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From the University of Illinois Health Service Department, Urbana.

Whether or not this regulation is governed or determined by the carotid sinus, or initiated through the neurogenic arc, or by an intrinsic myogenic factor or unknown regulatory centers, or a combination of these factors has not been conclusively proved. The vasopressor effect of certain hormonal secretions, particularly adrenalin, is well known. Zipf<sup>6</sup> and Goerner and Haley<sup>7</sup> have produced some evidence that depressor substances may also be present in the body fluids.

### SUMMARY

Students were divided into high, normal, and low blood pressure groups, a careful history taken on each, and the blood pressure reactions to a standard exercise test were recorded.

1. The increase in the systolic blood pressure following exercise was greatest in the high blood pressure group.

2. The systolic pressure after exercise in the hypertensive and hypotensive classes returned to normal more slowly than did the normal group.

3. The diastolic pressure during exercise fell on the average about as far below the basal level as the diastolic rose above the basal level with the cold test. This pressure returned to the original level somewhat more slowly in the hypertensive group.

4. There was a far greater difference between the usual or regular systolic blood pressure and the basal blood pressure in the hypertensive class than between those levels in the normal and low pressure groups. This criterion is a definite aid in discovering those cases in which the blood pressure should be checked more frequently.

5. The pulse rate following exercise returned to the basal rate within two minutes in the normal and low pressure subjects.

6. Vasomotor response from other factors plays a more important rôle in causing a systolic increase in blood pressure during exercise than does the pulse rate.

7. The same factors which govern the emotional status of an individual play an important part in the blood pressure reaction.

8. There is a definite hereditary factor in the regulation of blood pressure. The tendency toward essential high or low blood pressure is carried by the germ plasm from one generation to the next.

9. The amount of work or exercise apparently is not an etiological factor in the production of essential hypertensive blood pressure.

10. The quantity of food intake may be an etiological factor in producing high blood pressure, since there were two and one half times as many heavy consumers of food in this class as in either of the other groups.

11. At least two or three subsequent rechecks should be made before a person is classified into the hypertensive or hypotensive group. This will prevent worry and anxiety in certain patients, and will be of considerable value to the physician in arriving at a correct diagnosis.

about 8.5 per cent of the normal and low pressure groups had a diastolic decrease of 21 to 30 mm. as compared to 18.7 per cent of the hypertensive class. Some observers have failed to find a decrease in the diastolic pressure following exercise. The decrease is very definite and it is difficult to understand just why some of the investigators were unable to discover it.

The systolic pressure following exercise returned to the basal level within 5 minutes in 100 per cent of the normal group as compared to only 78.8 per cent of the high pressure group and 74.8 per cent of low pressure groups (table 2). The diastolic pressure which fell during exercise rose to the basal level within 5 minutes in 100 per cent of the normal and hypotensive subjects as compared to only 84 per cent of the high blood pressure group (table 2).

TABLE II  
Time for Blood Pressure to Return to Basal Level after Exercise

Blood Pressure	Time in Minutes								
	0	1	2	3	4	5	6	7	8
<i>High</i>									
Systolic.....			10.4*	24.2	26.3	17.9	14.7	4.2	2.1
Total†.....			10.4	34.6	60.9	78.8	93.5	97.7	99.8
Diastolic.....		2.1	14.7	27.3	25.2	14.7	11.6	4.2	
Total.....		2.1	16.8	44.1	69.3	84.0	95.6	99.8	
<i>Normal</i>									
Systolic.....			14.2	34.0	25.7	25.7			
Total.....			14.2	48.4	74.1	99.8			
Diastolic.....	5.8	8.8	23.5	17.6	26.5	17.6			
Total.....	5.8	14.6	38.1	55.7	82.2	99.8			
<i>Low</i>									
Systolic.....		8.3	8.3	16.6	25.0	16.6	8.3	16.6	
Total.....		8.3	16.6	33.2	58.2	74.8	83.1	99.7	
Diastolic.....	8.3	25.0	16.6	8.3	16.6	25.0			
Total.....	8.3	33.3	49.9	58.2	74.8	99.8			

\* All figures expressed in per cent of cases studied.

† Represents accumulative total per cent of students for each subsequent minute.

When the blood pressure variations for the three groups are calculated for each time period (figure 1), the following information was apparent:

1. The increase in the systolic pressure following exercise was greatest in the high blood pressure group.
2. The systolic pressure in the hypertensive and hypotensive classes returned to normal more slowly than did the normal group.
3. The diastolic pressure, which decreased, returned to the basal level somewhat slower in the high blood pressure subjects (figure 2).

The pulse rate following exercise in all the normal and low pressure cases returned to the basal level within two minutes. The pulse rate also fell

# THE TREATMENT OF ILLNESS OF EMOTIONAL ORIGIN BY THE INTERNIST\*

By EDWARD WEISS, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

BETWEEN the small number of obviously psychotic people whom an internist sees and the larger number of patients who are sick solely because of organic disease are a vast number of sick people who are not "out of their minds" and yet who do not have any definite bodily disease to account for their illness.

It is reliably estimated that about one-third of the patients who consult the internist fall into this group. These are the so-called purely functional problems of medical practice. Approximately another third of the patients who consult an internist seem to have symptoms that are in part dependent upon emotional factors even though organic findings are present. The latter group is even more important than the first from the standpoint of diagnosis and treatment. These psychosomatic problems are often very complicated and because serious organic disease may be present the psychic factor is capable of doing more damage than in the first group. For example, while the neurotic with a normal heart may suffer a great deal subjectively and may even have a disturbance of the cardiac function, marked by various forms of arrhythmia, the heart, certainly in the majority of such patients, remains structurally healthy. But the neurotic patient who has organic heart disease may add a real burden to the work of his heart either through constant tension of psychic origin or more especially by means of acute episodes of psychic origin and thus may hasten a cardiac breakdown which, without psychic stress, in many cases might be indefinitely postponed.

The figures that I cite will differ, of course, depending upon the psychosomatic training of the observer, but those that I have given are average figures and are now widely accepted. If, for example, the internist is a die-hard organicist who believes that every illness has an organic basis which will show up sooner or later "if studies are only thorough enough," the figures given by such an observer will differ from those of the psychosomatically trained physician who establishes the diagnosis of a functional disorder not simply on the basis of exclusion of organic disease but on positive findings from personality study as well. The latter recognizes that neurosis has its own distinctive features to be discovered by a study of the emotional life and that only in this way can serious errors in diagnosis and treatment be avoided. In this connection let me again emphasize that just as we cannot limit ourselves simply to the exclusion of organic disease in dealing with the purely functional group, so even more importantly in the second group is there the necessity for not resting content with the finding of an organic

\* Read at the Cleveland meeting of the American College of Physicians April 5, 1940. Department of Medicine, Temple University School of Medicine.

rapidly in the hypertensive class, but on the average did not reach the original rate for 3½ minutes after the exercise was discontinued. The average pulse rate increase after exercise was 30, 34, and 30 beats per minute for the high, normal and low pressure groups, respectively (table 3). The increase in the

TABLE III  
The Summarized Effect of Exercise upon Blood Pressure

	High Blood Pressure		Normal Blood Pressure		Low Blood Pressure	
		P — B.P.		P — B.P.		P — B.P.
Increase in systolic pressure—mm. Hg.	48		37		23	
Decrease in diastolic pressure—mm. Hg.	15		12		13	
Increase in pulse per minute	30		34		30	
Limit cases—showing increase in pulse and systolic B.P.		6 — 60 36 — 24		54 — 18 18 — 40		22 — 28 18 — 40

blood pressure cannot be attributed to this factor alone, since many cases had a marked increase in the systolic blood pressure with only a slight increase in the pulse rate, and vice versa. For example, note the variations of the pulse and corresponding blood pressure increase of the limit cases (table 3). In one case, the pulse only increased 6 beats per minute, yet the blood pressure increased 60 mm. Hg. At the other extreme, in one of the normal subjects, the maximum pulse increase was 54 beats per minute, yet the maximum blood pressure response was only 18 mm. Hg increase. The vaso-motor response from other factors appears to play a more important part in the production of the increased pressure than the increased pulse can account for.

TABLE IV  
Summarization of Blood Pressure Variations from the Basal Level

Blood Pressure	Systolic Blood Pressure						Diastolic Blood Pressure					
	L. B. P.*		N. B. P.*		H. B. P.*		L. B. P.		N. B. P.		H. B. P.	
	Mm. Hg	Rise Mm. Hg	Mm. Hg	Rise Mm. Hg	Mm. Hg	Rise Mm. Hg	Mm. Hg	Ave. Change Mm. Hg	Mm. Hg	Ave. Change Mm. Hg	Mm. Hg	Ave. Change Mm. Hg
Basal B.P.	99		116		136		70		74		80	
Usual B.P.	104	5	123	7	164	28	75	5	77	3	87	7
B.P. after Exercise	122†	23	153	37	184	48	57	13	62	12	65	15
B.P. with Cold Test	110‡	11	126	10	154	18	81	11	88	14	96	16

\* L. B. P. indicates low blood pressure, N. B. P. indicates normal blood pressure, H. B. P. indicates high blood pressure.  
† Figures indicate average maximum blood pressure after exercise. Under each column mm. Hg.  
‡ Figures indicate average maximum blood pressure with cold test. Under each column mm. Hg.



Very frequently following "thorough study" by means of the usual medical history, physical examination and laboratory investigation, some "pathological curiosity" is discovered which really has nothing to do with the illness and the patient is then treated as though organically diseased, is submitted to unnecessary medical or surgical treatment, which, in many instances intensifies the neurotic condition.

When emotional factors are associated with actual organic disease too little attention is paid to the emotional factors. The feeling exists and the statement is made that "the physical findings are sufficient to account for the illness." Again there are many physicians who pay lip-service to the question of psychic factors in illness by referring to the study and treatment "of the patient as a whole." They feel that they have done their duty to the study of the emotional life if they ask the patient if he is worried about anything and receive a negative reply. The point will be considered later that the patient is sick just because he is not aware of the things that are disturbing him. In other words the psychic material is forceful just because it is unconscious and is seeking another mode of expression. These are the same physicians who are apt to remark "but he doesn't look neurotic," perhaps believing that such a patient should by his general apprehension or by evidences of physical nervousness, betray the fact that he is neurotic. Unfortunately, most neurotics do not show any evidence of neurosis in their appearance, nor is the approach to their emotional problem so simple that the direct question—"are you worried about anything"?—will produce material of importance.

### EMOTIONAL PROBLEMS

We know that these patients have been badly handled. Can we do any better? What is the matter with them and how should they be treated? Before attempting to answer these questions, let me quote from a letter received from an internist with whom I had some correspondence on this subject: "it seems to me extremely doubtful if education of the doctor along these lines is the answer to the problem. To delve into the personality of the patients who need this sort of study requires much more time, tact and patience than most practitioners have and we cannot refer any considerable number to psychiatrists. Furthermore, as you know, the accessibility of these facts varies very often with the intelligence of the patient. Even when the emotional set-up has been deciphered, you will have to admit that you would find very much the same impasse if you were up against the same situation yourself. In other words, while some doctors may be able to analyze these neurotic factors, generally speaking very few can alter them. And it has been my experience that understanding a situation is not always tantamount to solving it." I know you will agree that these are important questions and I shall try to answer some of them.

First of all let me say that these patients are suffering from disturbances

upon some structural or physiological phenomenon of the autonomic nervous system, or endocrine function, or a combination of these factors, which are passed through the germ plasma from one generation to the next. There were 35.4 per cent of those students in the high pressure group who were heavy eaters, as compared to 14.8 and 14.3 per cent of the normal and low pressure subjects. As shown by the same table, it would appear that the amount of exercise or work is of little importance as a causative factor in the production of essential hypertension.

TABLE VI  
Results of Reëxamination of Students with Abnormal Systolic Blood Pressure  
upon Entrance Physical Examination

Blood Pressure	Above 150 Mm. Hg Upon Entrance		Below 104 Mm. Hg Upon Entrance	
	No. of Students	Per Cent of Students	No. of Students	Per Cent of Students
Remained unchanged . . . . .	96	24.8	56	17.6
To normal at 1st recheck . . . . .	251	64.8	192	60.5
To normal at 2d recheck . . . . .	25	6.4	69	21.7
To normal at 3d recheck . . . . .	15	3.9	0	0
Total rechecked . . . . .	387		317	
Not rechecked . . . . .	132	25.4	74	18.9
Total . . . . .	519		391	

To classify a patient as a hypertensive case after one blood pressure test cannot be condemned too strongly. The fallacy of so doing can be understood by the results obtained in our study (table 6). Note that the blood pressure of 64.8 per cent of the students with a systolic pressure above 150 mm. at the time of their entrance physical examination was normal at the time of the first recheck. After a third observation, 75 per cent were well within normal limits. Certainly, the excitement, nervousness, sense of uncertainty, new environmental adjustments, or other psychological effects must have been the etiological factors in producing most of these high systolic pressure readings. Riesman<sup>4</sup> and Grollman<sup>5</sup> have shown that such factors affect blood pressure. Just how this action occurs is still a matter of conjecture. Is it due to stimulation of the endocrine glands? Is it due to the autonomic nervous system alone with a resultant spastic constriction of the arterioles from psychic stimulation? Or can it be explained by the intrinsic myogenic capacity for the contraction and dilatation of the blood vessels? When the hypotensive subjects returned for their recheck, 82.2 per cent were within normal limits.

The autonomic nervous system is in a state of balance in normal persons under normal conditions. When the sympathetics and parasympathetics are in a state of equilibrium, a normal blood pressure results. When this balance is disturbed and more impulses are sent over the vasopressor or vaso-depressor fibers respectively a hypertensive or hypotensive state ensues.

sured the patient that no physical disease is present in the first instance, or that it is present to a certain extent in the second group, but that *the disability is out of proportion to the disease*, it is usually easy by examples of psychic causes for such physiologic disturbances as blushing, gooseflesh, palpitation, diarrhea, etc., to make the patient understand that a disturbance in his emotional life may be responsible for the symptoms. Then important clues for this disturbance can usually be found by encouraging a discussion of problems centering around vocational, religious, marital and parent-child relationships. This is usually best accomplished indirectly rather than by direct questions. The more one can persuade such a patient to talk about "his other troubles" the sooner do we come to an understanding of "the present trouble." The greater our success in switching the conversation from symptoms to personal affairs, the sooner do we come into possession of the real problem disturbing the patient. We are all familiar with the patient who is preoccupied with his bowel function and wants to talk about nothing else, whose whole life really seems to surround his daily bowel movement. It is the physician's duty tactfully to switch him from a discussion of his symptoms to a discussion of his personal life. It is not necessary to inform the patient that he is undergoing psychological treatment. Simply get him to talk about himself as a person rather than as a medical case. In adults domestic problems and professional and business relationships play a large part in functional illness. In young, unmarried people, family relationships, choice of a career, and often religious and sexual problems are important topics for discussion.

### ORGAN LANGUAGE

A method of helping patients to understand their symptoms which I find useful is based upon the symbolism of symptoms. I often say to them that if they cannot find an outlet for tension of emotional origin by word or action, the body will find a means of expressing this tension through a kind of "organ language." For example, if a patient cannot swallow satisfactorily and no organic cause can be found, it may mean there is something in the life situation of the patient that he "cannot swallow." Nausea in the absence of organic disease sometimes means that the patient "cannot stomach" this or that environmental factor. Frequently a feeling of chest oppression accompanied by sighing respirations, again in the absence of organic findings, indicates that the patient has a "load on his chest" that he would like to get rid of by talking about his problems. The patient who has lost his appetite and as a consequence has become severely undernourished, the so-called anorexia nervosa, which in its minor manifestations is such a common problem, is very often emotionally starved just as he is physically starved. The common symptom fatigue is very often due to emotional conflict which uses up so much energy that little is left for other purposes. Again emotional tension of unconscious origin frequently ex-

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sexuality to neuroses. Ever since the introduction of the epoch-making studies of Freud to the problems of neurosis, medicine has misunderstood his conception of sexuality. He has often been quoted to the effect that disturbances in genital activity are the sole cause of the neuroses. This is quite far from the truth. It is rather that difficulty in the sexual sphere appears as a revealing index to a neurotic personality and can be looked upon in that light. In other words, in much the same manner that urea retention serves as an index to an impending uremia, so do disturbances in the sexual life of the individual, such as varying degrees of frigidity in the female and varying degrees of impotence in the male, serve as a reliable index to the kind of a personality that is very liable to develop a neurosis. Here again, I must advise you to steer the conversation by means of indirect questioning and to listen rather than talk. This is especially important in regard to sexual problems and the more experience I have with patients the less I find it necessary to question them directly regarding these intimate matters. Sexual difficulties are rarely in themselves the cause of the kind of illness we have been considering; when they are important and the patient has a satisfactory relationship to the physician, sufficient confidence will eventually be gained to permit discussion of these intimate matters. In women questions regarding menstruation and child-bearing will often lead naturally to such a discussion.

In this connection let me suggest a cautious attitude in regard to marital maladjustments out of which situations symptoms often arise. The better these problems are understood from the standpoint of personality study the clearer it becomes that serious emotional maladjustment often stands behind the marital problem. Consequently casually to give advice regarding marriage and childbearing, divorce and extra-marital relationships as short cuts to involved emotional problems is to assume knowledge beyond present human understanding.

### PSYCHOTHERAPY

And now to come back to one of the questions raised by the internist who wrote to me regarding these matters, "suppose you do find something of importance in the emotional life of a patient, some conflict that is causing illness, what can you do about it? What good does it do the patient to know?" First of all, it is often a great help to the patient to know that the ailment is not organic in origin but is due to a disturbance in his emotional life. When a neurotic symptom is divorced from a fear of organic disease, cancer for example, it loses its force and then the slogan "carry on in spite of symptoms," often helps the patient a great deal. This is especially true if the psychological approach that I have discussed is combined with the study and the emotional background of the illness is made clear to the patient. This brings us to the question—"what then is psychotherapy?" Too often it is assumed to be something vaguely referred to as "the appli-

lesion. The day is near at hand for the final outmoding of the *either-or concept* (either functional or organic) in diagnosis and to place in its stead the idea of how much of one and how much of the other, that is, how much of the problem is functional and how much is organic. This is truly the psychosomatic concept in medicine.

To dispose of the first question that is often asked in such a discussion as this one—should the internist treat illness of emotional origin?—the answer is that he must. The problems are so numerous in his practice and the interrelationships of psyche and soma are so intimate and often so indissoluble, that he cannot avoid them. The question is whether by recognizing the important part that they play and by giving them more attention we can do a better job.

### PRESENT TREATMENT

When we review our present treatment of these patients we find that the first group are commonly told that no organic disease is present, that the whole thing is "functional" and are often dismissed without further care only to land eventually in the hands of some irregular practitioner or quack healer. Certainly in dealing with many of these patients, it is necessary to do more than assure the patient of the absence of physical disease. We will come back to this point later.

Worse than this the physician sometimes takes the attitude that the illness is imaginary, or that the patient is malingering, or assumes in some vague way that the patient is deliberately responsible for the illness. He refers to such patients slightlying as neurotics or lumps them all together as neurasthenics. I do not suppose it is necessary to remind this audience that these illnesses are just as real as cancer and that in no sense do they represent malingering. Before we can accomplish very much in this field we must do two things: one, correct our own attitude toward these illnesses so that we can take away from people the feeling that it is reprehensible to have an illness of emotional origin; and two, we must educate ourselves so that we can apply the same precise terminology to illness of emotional origin that we have, for example, in cardiac disease. It was only with more exact nomenclature that we made rapid advance in the cardiac field and the same will be true in the psychosomatic field.

Sometimes the patient is told that the physician does not *think* that anything is the matter but suspicion is cast upon some organ or system which needs watching and care. For example, the patient with symptoms referred to the heart region is told that his heart is all right but nevertheless he is cautioned to rest, medicine is given, and each time that he visits the physician his heart is examined again. We will consider this point later, but here it may be emphasized that in dealing with the majority of functional problems we must examine thoroughly, satisfy ourselves as to the absence of organic disease and then stop examining with the firm statement that "you do not have organic disease."

Such knowledge and such an approach will frequently save the patient from unnecessary, troublesome and expensive medical or surgical treatment with a resulting further degree of invalidism.

At this point let us consider some of these principles as applied to a psychosomatic problem. I think this can best be done by citing an illustrative case.

#### CASE REPORT

A white man, aged 37, first seen in March 1938, complained of "a heart condition," insomnia, tiredness and dizziness, inability to relax, rapid heart action, missed beats and sweating, and, according to the physician who referred him, suicidal tendencies.

The heart murmur had been discovered in school at the age of 12. He does not recall that any particular attention was paid to it at this time but in high school he was taken off of the ball team because of "an athletic heart." Thus he grew up with the idea that there was something seriously wrong with his heart.

At the age of 29, while swimming in an indoor pool, he had a sudden attack of palpitation, which was called a "heart attack" by his physician, and several days of complete bed rest were advised. On two subsequent occasions he also had the same kind of an attack; one attack terminated in a vomiting seizure. The other symptoms mentioned above have also been present since that time. He has seen many doctors, has considerably limited his activities and, according to his statement, has not wanted to marry because of his heart condition.

Just before coming to me he had suffered much from insomnia and at lunch the day before he had had rapid heart action and sweating, had felt dizzy and faint, and had a very heavy feeling in his chest. He had been nervous and jittery since. He became so desperate that he threatened suicide.

The physical examination showed a robust white man with perhaps slight cyanosis of the lips but no dyspnea and no clubbing or jaundice. The heart action was forceful. There was slight scoliosis which was responsible for slight displacement of the heart to the left; the organ did not seem enlarged. The sounds were well heard and seemed normal except for a slight systolic murmur in the third left interspace. There was no thrill. The remainder of the physical examination was negative.

Ordinary laboratory studies were within normal limits. There was no evidence of impairment of cardiac function and the response to effort was normal. I concluded that we were dealing with a congenital lesion, probably ductus arteriosus, which had not affected the working of the heart.

In 1934 and again in 1936 the patient was studied by Dr. Hugo Roesler to whom I am obliged for permitting me to use the following notes:

"1934. Mild cyanosis of the lips. Heart not enlarged. The apex is rather diffuse and a double wave short systolic retraction is noted. The first apical sound is split; no thrill. In the third left intercostal space there is a low, soft, deep-seated systolic murmur. The pulmonic second sound is hardly audible. The murmur is not influenced by respiration. Blood pressure systolic 138, diastolic 95. Rate 80 per minute. "Roentgen-ray. The heart is normal in size; there is moderate prominence and increased systolic pulsation of the pulmonic arc.

"Electrocardiogram: Regular sinus rhythm; normal auriculoventricular conduction time. Moderate slurring of the initial deflection in Leads II and III. The T-waves are positive in all three leads. A Q-wave is present in Lead III.

in their emotional lives; that is, the illness is of psychological origin and can be satisfactorily studied and treated only from a psychological standpoint. It is true that the ill health arises from long standing dissatisfactions in the business, social or home life of the individual and that this failure of adjustment to environment is manifested by a disturbance in some part of the personality, either as bodily symptoms of various kinds, capable of mimicking almost any disease, or as affections of the spirit resulting in attacks of anxiety, obsessions, phobias, depression and other disturbances of mood. What is not so generally realized is that the mere discovery of the so-called dissatisfactions or unpleasant occurrences in the life situation of the individual is not a sufficient explanation nor even an adequate indication of the psychic background of the illness. In other words, besides excluding organic disease and besides the effort to tie up the occurrence of an unpleasant episode and the beginning of the illness from the standpoint of a time relationship, it is of the greatest importance to know the patient's ability to adjust to such situations, his pattern of reaching to them, the degree of anxiety in his make-up, the nature and seriousness of his conflicts. Personality study is necessary if we are to establish a specific relationship of the psychic situation to the personality of the individual. Just as the typhoid bacillus is specific for typhoid fever, depending of course upon the susceptibility of the individual, so the psychic event must be specific for the personality structure of the person. To make such studies one must have some training in psychopathology. When psychopathology is given an equal place with tissue pathology in our medical curriculum and is as well taught we will finally realize that psychotherapy is an integral part of our medical discipline.

#### PSYCHOSOMATIC STUDY IN ILLNESS

Can any advice be given as to how to proceed with this kind of a study? In a general way it may be stated that in addition to the physical study it consists simply in getting to know the patient as a human being rather than only as a medical case. Too often, as already stated, the patient is looked upon as a physiological mechanism and is studied by means of medical history and physical examination aided by "instruments of precision" and chemical tests. Tape measures and test tubes carry the erroneous notion of exactness and thoroughness—erroneous because the emotional life of the individual, which may hold the key to the solution of the problem, is not investigated or at best inadequately so.

Probably the best way to deal with these patients is first to satisfy ourselves and establish their confidence by a thorough medical history which must contain more information regarding the family and social background of the patient than our present histories do; then a complete physical examination and such laboratory tests as are necessary to exclude organic disease or to establish the precise nature of the organic problem and the amount of disability which it in itself is capable of causing. Having as-



I explained to the patient that he had a congenital lesion of the heart that in no way inconvenienced the working of that organ and I assured him that his symptoms had nothing to do with this "pathological curiosity." Gradually I succeeded in convincing him that his heart was not seriously diseased, that he was able to engage in many activities that he had denied himself, and that no harm would come to his heart as a result. The anxiety attacks became less intense and came at greater intervals and his sleeping was much improved. Occasionally an attack would occur and when it did all of his doubts regarding his heart would return. This would necessitate further reassurance along the lines already indicated. At the same time an effort was made to show the patient some of the psychic reasons for his illness. Attacks would frequently occur when family situations arose which stirred up his aggression. Because of this throttled aggression he was checkmated in all directions. His solicitude for his father and step-mother would not permit him to express any indignation to them or to his brothers. He was afraid to work hard or to engage in any athletic activities because of his heart, and even his sexual function was impaired. Hence it was obvious that we were dealing with a severely inhibited individual whose normal aggression could find no outlet. Nevertheless, as he gained confidence from reassurance and some insight into the emotional background of his illness he became a more effective and more contented person, engaged in longer hours of harder work and indulged himself in other regards.

However, his attention had been so fixed upon his heart that the slightest recurrence of symptoms would bring some of his old doubts back again. Once more reassurance, like a dose of medicine, would improve his condition. The advice of physicians to rest and to limit his activities had played into his unconscious need for illness. Just the opposite kind of tactics, teaching him to ignore his heart so far as it was possible for him to do so, to carry on his activities in spite of symptoms, together with the effort to show a relationship between his attacks and his emotional life resulted in a considerable degree of improved health and happiness so that he became more efficient in his work and more effective in his social contacts.

### COST OF PSYCHOTHERAPY

Now we come to the question of time, effort and the expense of psychotherapy. Certainly it is true that all of this takes time and effort and must be paid for, yet when we look into the time, effort and expense that have been expended by many patients or by institutions taking care of these patients in the usual medical approach, we realize that an hour or two well spent in a discussion of the life situation of such patients would obviate a great deal of this other expense. In the outpatient medical department we are making a study of patients of this kind, the criterion for selection being a chart one inch thick. It is amazing what the total expense of a great many of these unnecessary studies amounts to so far as the institution is concerned, and of course the same thing is true in the case of private patients. I think the day is close at hand when we will regard some of these thick-chart patients, this poly-physical approach, with the same amusement and disdain with which we now regard the polypharmacy of a bygone age in medicine. Hospitals are beginning to understand that it is not only intelligent but economical to utilize the service of a psychiatrist in the general medical division and this same idea could be applied with great benefit to the much discussed medical insurance plans.

presses itself as muscle tension giving rise to aches and pains and, sometimes, these are represented by sharp pains such as atypical neuralgias. An ache in the arm sometimes means that the patient would like to strike someone, but is prevented from doing so by the affection or respect that is mingled with his hostility, rather than representing the response to a focus of infection. May I suggest that the next time you deal with an atypical neuralgia of arm or face you look for "focal conflict" as well as "focal infection." Itching for which no physical cause is found very often represents dissatisfaction with the environment which the individual takes out upon himself; martyr-like he scratches himself instead of someone else. "All gone" feelings in the epigastrium, "shaky legs," even vertigo are common physical expressions of anxiety and the anxiety attack, so frequently called a "heart attack," gall-bladder disturbance, hyperthyroidism, neurocirculatory asthenia, hyperinsulinism, etc., is still far from being understood in general clinical medicine in spite of the fact that Freud described it more than 40 years ago. I would like to give many more examples and cite illustrative cases but time does not permit. Only one more point before concluding this part of the discussion and that is that the gastrointestinal tract is above all other systems the pathway through which emotions are often expressed in behavior. As has been well said, the abdomen is the sounding board of the emotions. And certainly it is not very difficult to understand why this should be so. In early life the infant derives emotional satisfaction as well as sustenance from his feeding. Feelings of affection and anger get bound up with the feeding process and these associations may become deeply buried in the mental life of the individual but are never lost. If then the need for food and need for affection are indissolubly bound in the unconscious emotional life of the patient, we are certain to see a great many individuals who on the surface are grown up adults but who underneath express by means of the stomach their infantile desire for love and affection. Then frustration in real life frequently results in disturbances of muscle tension and secretion to provide the background for functional gastrointestinal disturbances.

This whole approach can be summed up in the following fashion: *if symptoms exist without an organic basis or, if organic disease fails to explain the symptoms completely, look for their meaning from the standpoint of behavior.*

Such an approach can be applied to a wide variety of symptoms and can be utilized very generally in talking with patients. Nor does it require a very high degree of intelligence on the part of the patient to follow this simple explanation. Patients in the clinic as well as those in the private ward can be dealt with in this fashion and as you well know are just as susceptible to these functional disorders.

#### SEXUAL FACTORS

This is too large a subject to cover in a short paper, but one point of special importance does deserve consideration and that is the relation of

# HEMATOLOGIC ASPECTS OF SPACE CONSUMING LESIONS OF THE BONE MARROW (MYELOPHTHISIC ANEMIA)\*

By STACY R. METTIER, M.D., F.A.C.P., *San Francisco, California*

IN the medical literature of recent years attention has been called to a type of anemia usually associated with immature red and white cells in the peripheral blood. This anemia has been described under such titles as myelophthisic anemia,<sup>1</sup> leuko-erythroblastic anemia,<sup>2, 3</sup> myelosclerosis associated with a leukemoid blood picture,<sup>4</sup> megakaryocytic myelosis with osteosclerosis,<sup>5</sup> and, simply, a leukemoid reaction.<sup>6</sup> The data reported in the various cases so described suggest that the underlying structural changes of the marrow were essentially sclerotic in character.

During the past several years a large number of patients with anemia have been examined at the University of California Hospital whose blood streams contained abnormal cells and whose clinical pictures presented difficult diagnostic problems. In the course of the study of a group of these patients, it was observed that the hematologic data were similar. On biopsy of the sternum a varied pathologic change was found but the patients had in common a marrow replaced by abnormal tissue. Because of the difficulties encountered in the diagnosis of the conditions causing replacement of marrow, the paucity of hematologic data in the literature and the confusion arising from their classification, the hematologic aspects of space consuming lesions of the bone marrow are discussed in this paper.

## METHOD OF EXAMINING THE BONE MARROW

Under local anesthesia an incision was made through the skin and subcutaneous tissues. A "button" of bone having a diameter of 15 mm. was removed with a trephine. Specimens of marrow were removed with a curette and spread preparations were made immediately on cover slips. These were stained according to the method of Wright or Giemsa. Other pieces of marrow tissue were fixed in Zenker's fluid containing 5 per cent glacial acetic acid and at the appropriate time were embedded in paraffin, sectioned and stained with hematoxylin and eosin.

## REPORT OF CASES

### GENERALIZED OSTEOSCLEROSIS, AMYLOID DISEASE OF LIVER AND KIDNEYS, TERTIARY SYPHILIS

*Case 1.* A. P., a white man, aged 50, was admitted to the University of California Hospital on August 23, 1938, complaining of weakness and dyspnea. Because

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cation of the art of medicine." This defies analysis but seems to represent a combination of the experience and common sense of the seasoned practitioner, an intuitive knowledge of people plus the cultivation of a charming bedside manner, such trifles as serving food in attractive dishes, and the generous use of reassurance. The psychological approach in medicine, essential for psychotherapy, consists of something more. It is a medical discipline to an equal degree with internal medicine itself. It is an effort to understand the personality structure of patients, the mental mechanisms which are at work, and the specific relationship of psychological situations in the precipitation of the illness.

Reassurance in the majority of instances, unless combined with an analysis of the illness from the standpoint of the behavior, gives only temporary help and depending upon the degree of anxiety has to be constantly repeated, like a dose of digitalis in a failing heart. Closely allied to reassurance is another superficial treatment that rarely results in more than temporary help, i.e. environmental manipulation without any attempt to give the patient insight into his conflicts. Real psychotherapy, which is directly the opposite of simple reassurance, tries to make the patient understand the meaning of his symptoms and the nature of his conflicts. It is a reëducational process and when properly done leads to sufficient emotional development so that the necessity for symptom formation is abolished. The best example of this kind of psychotherapy is psychoanalysis, but for various reasons this method cannot be applied directly to the majority of patients. Nevertheless, psychoanalytic insight and guidance in management combined with reëducation and reassurance prove adequate for the majority of functional disturbances. Between simple reassurance at one end of the scale and adequate psychoanalysis at the other, there are all degrees of psychotherapy which can be applied depending upon the degree of illness and the circumstances of the patient. It is my contention that every physician should be trained in psychological medicine so that he may be able to understand and manage the many emotional problems that are presented to him daily. In addition I think some internists will adopt psychosomatic medicine as a subspecialty in the same way that others interest themselves chiefly in cardiology, gastroenterology, etc.

As my correspondent stated, a considerable number of these patients cannot be sent to psychiatrists. Nor is it necessary. Another way of stating the problem is to say that there is major and minor psychotherapy just as there is major and minor surgery. Many physicians who practice general medicine feel themselves capable of doing minor surgery, but only a few have the skill to attempt major surgery. They would not permit themselves to attempt something for which they are not prepared. This is just as true in regard to psychotherapy. The general physician must be able to treat the minor ailments but he must be able also to recognize when the problem is beyond him and then refer the patient elsewhere for major psychotherapy.

*Course of Illness.* Treatment consisted of the oral administration of a saturated solution of potassium iodide and the parenteral administration of bismuth salicylate in doses of 0.2 gm. at weekly intervals. While in the hospital the patient gained 2 kg. in weight, but there was little change in the red blood cell or hemoglobin values or in the size of the liver.

#### GAUCHER'S DISEASE WITH SPLENOMEGALY AND REPLACEMENT OF BONE MARROW WITH KERASIN CELLS

*Case 2.* E. F., a Jewish female, aged 54 years, was first seen on January 3, 1935. For two years she had been under the care of her family physician because of precordial pain, dyspnea and a generally enlarged abdomen. The attacks of pain had been relieved quickly with nitroglycerin.

*Physical Examination.* The patient appeared anxious and emaciated. She became dyspneic with slight exertion and had cyanosis of the lips and of the tissue beneath the finger-nails. The skin was of a "dusky" hue. The superficial lymph nodes were not enlarged. The gums receded about many of the teeth and bleeding points appeared along the gingival margin upon slight trauma. The heart was found greatly enlarged on percussion and the apex was at the anterior axillary line in the fifth inter-space. No cardiac murmurs could be heard. No râles were heard in the lungs. The blood pressure was 160 mm. of mercury systolic and 100 mm. diastolic. The abdomen protruded markedly and the skin was stretched tightly over it. A large smooth mass, presumably the spleen, was felt in the left side of the abdomen and extended into the pelvis and slightly to the right side of the mid-abdominal line. A second mass, presumably the liver, was felt on the right side of the abdomen, the edge reaching half-way between the umbilicus and the brim of the pelvis. There was pitting edema of ankles and feet.

*Laboratory Data.* On January 3, 1935, the blood count showed: hemoglobin 58 per cent (8.1 gm.) Sahli; erythrocytes 3,640,000; and leukocytes 1,300 per cubic millimeter. The differential count showed: segmented polymorphonuclear leukocytes 38 per cent; non-segmented leukocytes 23 per cent; polymorphonuclear basophiles 1 per cent; large lymphocytes 6 per cent; small lymphocytes 17 per cent; monocytes 10 per cent; myelocytes 4 per cent; 1 nucleated red blood cell per 100 white blood cells. The platelets were 90,000 per cubic millimeter. The volume of packed red blood cells was 24 mm.; the mean corpuscular volume was 79 cubic microns; the mean corpuscular hemoglobin concentration was 29 per cent; the mean corpuscular hemoglobin was 23 micrograms. There was marked poikilocytosis and anisocytosis of the erythrocytes.

*Course of Illness.* The patient remained under observation from January 1935 until June 1938. During this time the anemia and leukopenia persisted and the platelets varied from 30,000 to as high as 110,000. On occasions petechial hemorrhages appeared in the skin and blood oozed from the gums. In January 1938 the patient complained of constant pain in the region of the lower dorsal vertebrae. A roentgenogram of the spine showed collapse of the body of the ninth dorsal vertebra. The patient continued to have attacks of precordial pain and marked dyspnea with slight exertion. On June 8, 1938, during such an episode, she suddenly collapsed and expired.

*Gross Postmortem Examination.* The autopsy was performed by Dr. C. L. Connor. The body was that of a poorly developed, emaciated woman. The gums were swollen and evidences of small hemorrhages could be seen at the gingival margins of some of the teeth. On the right side of the face were several ecchymotic areas. The abdomen was tremendously distended. The legs were edematous and many petechial hemorrhages were present in the skin.

*Internal organs:* The abdominal cavity showed a smooth lining and contained about 1 liter of clear amber fluid. The left pleural cavity contained about 400 c.c. of clear fluid and the right about 300 c.c.

"Discussion. Congenital cardiovascular malformation, most probably patency of the ductus arteriosus; other malformations may be present but cannot be proved. The patient has had attacks of either sinus or auricular tachycardia and also attacks of what seemed to be auricular fibrillation. But these disturbances are not in connection with the anatomical malformation. There is no evidence of disease or dysfunction of the myocardium. Personality study is advised.

"1936. General findings, fluoroscopy and electrocardiogram unchanged. Blood pressure standing 120/60; recumbent 130/80. Conclusions as before."

### LIFE SITUATION

The patient was the next to the youngest in a family of nine children. His mother had died at the age of 47, when the patient was 13, of some "kidney condition"; she had been sick for years. The father shortly had married again and the patient now makes his home with the aged father and step-mother; all of the siblings have married and live away from home.

A short time before the patient became ill the father had had a stroke of apoplexy and had been a cripple but not an invalid since. He is now 72 and has high blood pressure. The patient supports his father and step-mother, receiving no help from the rest of the family, which he very much resents although he does not readily admit it. Conversations regarding his inability to marry indicate that not only his heart condition but the fact that he is responsible for the care of his sick father and step-mother is a deterrent; in other words he feels that he is sacrificing himself for his invalid father.

Another circumstance that seemed important was that following his father's stroke and just before the patient's first "heart attack" a man had been suddenly killed at his place of business and he felt that he had given the order to this man which resulted in his being in a certain spot at the moment that the accident occurred which resulted in his death. He could not forgive himself "for sending this man to his death" although it was obvious that it was a routine order in the ordinary conduct of the business. Nevertheless, guilt and self-accusation persisted. Further study which I shall not detail here indicated that this episode had reminded him of his father's stroke and had energized a psychic conflict in regard to his father, for it became clear that the excessive solicitude for his father covered unconscious hostility and fancied threats to his father's welfare awakened great anxiety in the patient. Anxiety not only disturbed his heart action but resulted in insomnia and excessive urination as well.

When disturbed "his chest (heart) would feel solid, heavy and hot; the left arm would ache and feel numb, the left hand was cold; the head felt swollen, the hair stood on end, he would drool saliva and urinate large quantities at frequent intervals." These were clearly the symptoms and signs of his pronounced anxiety. Insomnia seemed to disturb his efficiency as much as the concern over his heart. His attitude was a determination to go to sleep which, of course, resulted in just the opposite effect. He gave the impression of being not only a vigorous but a violent person with no outlet for his aggression. Thus he would dream a great deal about fighting and became much disturbed in witnessing athletic contests. When he visited my office he would stomp in and jerk the office chair before seating himself.

A symptom to which he apparently paid little attention but which was significant as a further indication of his neurotic difficulties was impotence which he said came on gradually shortly after he became ill. It was obviously of psychological origin because the physical examination was negative and the impotence would assert itself only at certain times and with certain women.

Hypertrophy of the heart and myocardial degeneration, ossified annulus fibrosus of the mitral valve. Generalized arteriosclerosis.

BONE MARROW SHOWING CARCINOMATOUS METASTASIS (SURGICALLY REMOVED  
CARCINOMA OF BREAST 11 YEARS PRIOR TO HOSPITAL  
ENTRY). SPLENOMEGALY

*Case 3.* I. A. P., a white American female, aged 58, entered the University of California Hospital on December 9, 1937, complaining of weakness, pallor, dyspnea and hemorrhages into the skin. She stated that 11 years previously her left breast had been removed because of carcinomatous degeneration. Since then frequent examination of the operative site by her physician and roentgenograms of the lungs had failed to reveal signs of local recurrence or metastatic foci in the lungs. Her symptoms began five months before entry when she first noted that she was easily fatigued. At that time her physician found that her hemoglobin was 40 per cent. Dyspnea, weakness and loss of weight had developed progressively since then.

*Physical Examination.* The patient appeared weak and emaciated. There was marked pallor of the skin and mucous membranes. An ecchymosis was present on the right forearm and petechial hemorrhages were seen in the skin of the lower extremities. Slight gingivitis was present, but there was no oozing of blood from the gums. The lymph nodes were slightly enlarged, particularly in the left axillary region. Moist râles scattered throughout the lungs could be heard on inspiration. A well healed operative scar was present in the left upper thorax and the left breast was missing. The heart was not enlarged on percussion but a systolic murmur was heard in the region of the apex. The abdomen was slightly protuberant. A firm, smooth mass with a notched border, presumably the spleen, was felt in the left upper quadrant of the abdomen. The liver was smooth and slightly tender and its edge was felt 3 cm. below the right costal margin.

*Laboratory Data.* The blood count showed: hemoglobin 23 per cent (3.3 mg.) Sahli; erythrocytes 1,770,000 per cubic millimeter; and leukocytes 5,400 per cubic millimeter. The differential count was: segmented polymorphonuclear leukocytes 30 per cent; non-segmented leukocytes 20 per cent; polymorphonuclear eosinophiles 2 per cent; lymphocytes 20 per cent; monocytes 1 per cent; myelocytes 19 per cent; normoblasts 30 per 100 white blood cells; platelets 25,000 per cubic millimeter. There were marked anisocytosis, poikilocytosis and polychromatophilia of the red blood cells. The mean corpuscular volume was 101 cubic microns and the mean corpuscular hemoglobin concentration was 32 per cent. Fluoroscopic examination of the chest revealed many lesions within the pulmonary parenchyma. Roentgenograms showed a highly advanced degree of a combination of osteolytic and osteoblastic new bone formation in the fourth and fifth lumbar vertebrae, in all the bones of the pelvis and in the upper six inches of the femur. Diagnosis was carcinomatous metastasis of the bones. The Wassermann and Kahn tests of the blood for syphilis gave negative reactions. Biopsy of sternal marrow: The marrow tissue was almost entirely replaced by wildly growing epithelial tissue accompanied by dense fibrous tissue. The epithelial cells were arranged in small sheets and groups; among these cells mitotic figures were seen. There were a few hematopoietic cells, mostly of the myeloid type. It was concluded that the sternal marrow showed carcinomatous metastasis.

MULTIPLE NEUROFIBROMATOSIS OF SKIN (VON RECKLINGHAUSEN'S DISEASE),  
BONE MARROW AND POSTERIOR CRANIAL FOSSA

*Case 4.\** T. B., a white American male, aged 39, entered the University of California Hospital on December 8, 1936, complaining of dizziness and headaches. He

\* This case is to be reported in detail at a later date.

The last hundred years in medicine have seen the structural concept of disease lead from morbid anatomy and cellular pathology to the bacteriological era and its great discoveries. Then came the period of biochemistry and metabolism which has led to the enormously productive endocrinology. We are just tapping the door leading to the era of psychological medicine which I am confident will make contributions of equal importance.

Medicine had its real beginning in the study of man at the dissecting table. Let us continue with the study of man not only as an anatomical and physiological mechanism but as a human being possessed of loves and hates, urges and passions capable of disturbing his soul and his body.



movement of any part of the body caused discomfort. Since the onset of illness he had been confined to his bed almost constantly because of weakness and pain.

*Physical Examination.* The patient appeared weak and cachectic. The skin and the mucous membranes were pale. The lymph nodes were not enlarged. The head was of normal contour and no tenderness was elicited on pressure. Many points of tenderness were noted over the ribs anteriorly, in the axillae, and over the sternum. No abnormalities were found in the heart or lungs. Neither the spleen nor the liver was enlarged. Pressure on the pelvic bones caused excruciating pain.

*Laboratory Data.* The blood count showed: hemoglobin 44 per cent (6.4 gm.) Sahli; erythrocytes 1,790,000 per cubic millimeter; leukocytes 5,200 per cubic millimeter. The differential count showed: segmented polymorphonuclear leukocytes 20 per cent; non-segmented leukocytes 23 per cent; eosinophiles 3 per cent; basophiles 3 per cent; lymphocytes 20 per cent; monocytes 5 per cent; myelocytes 9 per cent; plasma cells 17 per cent. The normoblasts varied from 1 to 7 per 100 white blood cells. Anisocytosis and poikilocytosis of the red blood cells were marked. The platelets were 200,000 per cubic millimeter. The blood uric acid was 4.6 mg. per 100 c.c. The Wassermann and Kahn tests for syphilis were reported negative. The blood serum protein showed: total 9.21 per cent; of this 2.5 per cent was albumin and 6.71 per cent was globulin; the ratio of albumin to globulin was 0.37. No Bence-Jones protein was found in the urine. Roentgenograms showed that the clavicles, scapulae, ribs, lumbar vertebrae, pelvic bones and upper parts of the femura contained innumerable "punched out" areas. The trabecular structure of the bones was altered so that striations were not visible and there was very little evidence of calcium. Conclusion: multiple myeloma.

Biopsy of sternum: Sections of sternal marrow removed for biopsy showed almost complete replacement of the cells normally present by a large mononuclear type of cell. The membrane of the cells was distinct. The cytoplasm was brightly eosinophilic and finely granular. The nucleus was large and occupied almost all of the cell; it was basic and contained coarsely divided chromatin material which was distributed largely about the periphery. Many of the nuclei contained nucleoli. Diagnosis: plasmacytoma.

### CLINICAL PICTURE

In many of the patients the symptomatology was poorly defined. The symptoms presented were variable but perhaps the most frequent was weakness. The onset was usually insidious. During the course of the illness some of the patients became distressed by palpitation and dyspnea. Evidences of hemorrhagic diathesis in the form of a generalized purpura or a petechial eruption was observed in three of the patients.

The physical examinations yielded a few striking findings. Most of the patients were poorly nourished and some appeared cachectic. The superficial lymph nodes were not enlarged. The spleen was enlarged in eight of the patients. In the patient with Gaucher's disease the spleen was of tremendous size.

Roentgen examination of the bony skeleton yielded interesting information. Abnormal findings were present in eight cases examined. Increased areas of density in the medullary cavities, osteolytic processes, rarefaction, alterations of the trabecular structure and a mottled appearance of the bones were some of the changes which suggested the presence of space consuming lesions in the bone marrow.

of anemia he had been given a transfusion of whole blood by his physician on January 17. This procedure had been repeated on March 15, May 17 and June 9. On June 10 a laparotomy had been performed for the purpose of examining the abdominal contents. The operator had noted that the liver was moderately enlarged and smooth, and appeared normal in color and consistency; the spleen was normal in size; the lymph nodes were not apparently enlarged; no tumor masses could be felt along the course of the gastrointestinal tract; and no stones were palpable in the gall-bladder. Despite the administration of transfusions, liver extract potent in pernicious anemia, large doses of iron and various vitamin preparations, the patient had continued to be anemic.

*Physical Examination.* On admission to the hospital the patient appeared very thin and emaciated. The lymph nodes were not abnormally enlarged. The teeth were carious and the margins of the gums showed evidence of infection. The heart was not enlarged on percussion and no cardiac murmurs were heard. The blood pressure was 122 mm. mercury systolic and 95 mm. diastolic. The abdomen was moderately protuberant and a smooth mass with a firm non-tender edge could be felt which extended 10 cm. below the right costal margin, 12 cm. below the xiphoid process and 4 cm. below the left costal margin. No other masses could be felt.

*Laboratory Data.* The blood count showed: erythrocytes 2,268,000 per cubic millimeter; hemoglobin 44 per cent (6.1 gm.) Sahli. The mean corpuscular volume was 97 cubic microns, the mean corpuscular hemoglobin concentration was 21 per cent and the mean corpuscular hemoglobin was 20 micrograms. The color index was 0.77. The leukocytes were 14,100 per cubic millimeter. The differential count showed: segmented leukocytes 61 per cent; non-segmented leukocytes 19 per cent; large lymphocytes 5 per cent; small lymphocytes 10 per cent; monocytes 3 per cent; myelocytes 2 per cent. The reticulocytes were 1.6 per cent. The platelets were 205,000 per cubic millimeter. The icterus index was 2 units. The urine contained a large amount of albumin but showed no evidence of a reducing substance with Benedict's reagent. The tuberculin test gave negative reactions to both human and bovine antigens in dilutions of 1 to 1000. The Mosenthal dilution and concentration test of kidney function showed a variation of only 0.002. The intravenous injection of phenolsulphonphthalein resulted in 68 per cent excretion in two hours. The blood Wassermann test was reported 4 plus positive; the Kahn test was also strongly positive. The spinal fluid Wassermann test was negative. Tests for amyloid disease with the dye congo red showed 100 per cent absorption in 1 hour. A test for liver function with bengol rose showed 50 per cent retention in 8 minutes and 23 per cent at 16 minutes (normal range). The total blood serum protein was 6.09 of which 1.34 was albumin and 4.75 was globulin; the albumin-globulin ratio was 0.28. Fluoroscopic examination and roentgenograms of the gastrointestinal tract failed to show any abnormalities. Roentgenograms of the right femur and the left humerus demonstrated an advanced osteosclerotic process in the marrow cavities. Films of the skull showed a similar process involving the cranial bones, the facial bones and the maxillae. According to a film of the chest, the heart, aorta and lung fields were within normal limits. The blood serum calcium was 10.28 mg. per 100 c.c. and the phosphorus was 22.02 mg. per 100 c.c. The basal metabolic rate was 14 per cent plus. A biopsy of the sternum was done and a button of bone 15 mm. in diameter was removed. There was no evidence of marrow cavity. Specimens of bone were fixed in Zenker's solution, decalcified, sectioned and stained with hematoxylin and eosin. Examination under the microscope showed a complete absence of the usual architecture of the bone marrow. The bone elements were greatly in excess of normal. There was evidence of slight erythropoiesis and much fibrosis between the spicules of bone. A few young forms of the white cell series were found. Diagnosis: Sternal bone marrow showing osteosclerotic changes and hypoplasia of erythropoiesis and myelopoiesis.

nuclear leukocytes. Myelocytes comprised from 2 to 43 per cent of the total cells, which in the presence of leukopenia indicates an absolute increase of considerable degree. Careful examination of the blood films failed to show the presence of myeloblasts.

The blood platelets were reduced in six of the patients. In three of the patients there was a distinct thrombopenia accompanied by purpuric manifestations, namely, spontaneous bleeding from mucous membranes, petechial hemorrhages into the skin, prolongation of the time required for a clot to form, and the subsequent formation of a soft non-retractile gel.

### STRUCTURAL CHANGES OF THE BONE MARROW

The photomicrographs shown in figures 1 to 5 correspond to case histories 1 to 5 respectively. Histologically the changes in the marrow were marked but varied in character depending upon the type of process involved. In each of the sections studied the normal orderly arrangement of the hematopoietic cells in the interstices of the fat was disturbed. The outstanding structural changes were: sclerosis of the marrow cavity by an ingrowth of connective tissue, displacement of marrow by conglomerations of tumor cells, and pressure atrophy of the tissue normally present by invasive or infiltrative lesions.



FIG. 1. Bone marrow showing osteosclerotic changes and hypoplasia of erythropoiesis and myelopoiesis.

**Heart:** The pericardium was greatly distended and contained a tremendously enlarged heart which weighed 548 gm. There were 800 c.c. of clear fluid in the pericardial sac. The visceral pericardium showed several roughened, fibrotic areas on the anterior surface and the coronary arteries were quite prominent and heavily calcified. The mitral valve was thickened and its ring contained a calcified and apparently ossified deposit which projected beneath the posterior leaflet of the mitral valve.

**Lungs:** There was no evidence of any disease process in the lungs.

**Liver:** The liver was greatly enlarged and weighed 3,650 gm. The cut surface was of a dull red-brown color and showed a multitude of thin, gray streaks which were thought to represent an increased amount of portal connective tissue.

**Spleen:** the spleen was tremendously enlarged and weighed 4,400 gm. It occupied the entire left half of the abdomen and extended into the pelvis. There were no adhesions about the spleen but rounded nodules about 2 cm. in diameter could be seen bulging up under the capsule. The cut surface was deep red and friable. Throughout the pulp were a large number of poorly defined, slightly raised tumor masses, some of which showed evidence of hemorrhage while others were greenish-yellow to red in color.

**Bone and bone marrow:** The sternal, costal and vertebral bones were quite soft and easily cut with a knife. The marrow appeared to be replaced by a very soft red hyperplastic tissue surrounded by a greatly thinned cortex. In some areas the marrow content was of a greenish-yellow color. The bodies of the ninth and tenth dorsal vertebrae were completely collapsed.

**Other organs:** The gastrointestinal tract, pancreas, kidneys, aorta, thyroid and adrenals showed no abnormalities.

*Microscopic Postmortem Examination.* **Spleen:** The sinusoids were pitted with cylindrical masses of large cells and the splenic pulp was almost completely obliterated. The large cells contained relatively small, round nuclei. The cytoplasm was composed of a faintly staining reticular material which appeared to contain vacuoles. Specimens stained with phosphotungstic acid hematoxylin showed more definitely the fibrillary material running through the cytoplasm. This structure seemed characteristic of Gaucher's disease and the material in the cells was apparently kerosin. The few splenic follicles that could be seen were represented by a small number of scattered lymphocytes.

**Liver:** The liver presented a most peculiar picture of well advanced cirrhosis in which the islands of liver cells remained in a fibrous tissue stroma. The connective tissue appeared to be of loose structure and between the fibrils here and there the characteristic cells of the type described in the spleen were seen. Accumulations of similar cells could be seen beneath the capsule and in some of the sinusoids.

**Kidneys:** There were some scars beneath the capsule and in the subjacent cortex there were fibrosed glomeruli. The arterioles showed well marked thickening and degeneration of the type associated with hypertension.

**Bone marrow:** This was active to the extent of moderate hyperplasia in which the erythroblasts and normoblasts predominated. Myeloid cells and megakaryocytes were seen in moderate numbers. The normal structure of the marrow was disarranged by groups of cells containing kerosin similar to those described in the spleen and the liver. These cells appeared in greatest numbers beneath the cortex of the bone.

**Pancreas:** There was some increase of interstitial connective tissue and occasional kerosin-containing cells were seen.

**Other organs:** No Gaucher cells were seen in the lymph nodes. No significant abnormalities were noted in the adrenals, ovary, thyroid or breast tissue.

*Postmortem Diagnosis:* Gaucher's disease with kerosin-containing cells in the spleen, liver, bone marrow and pancreas. Cirrhosis of the liver. Splenomegaly.

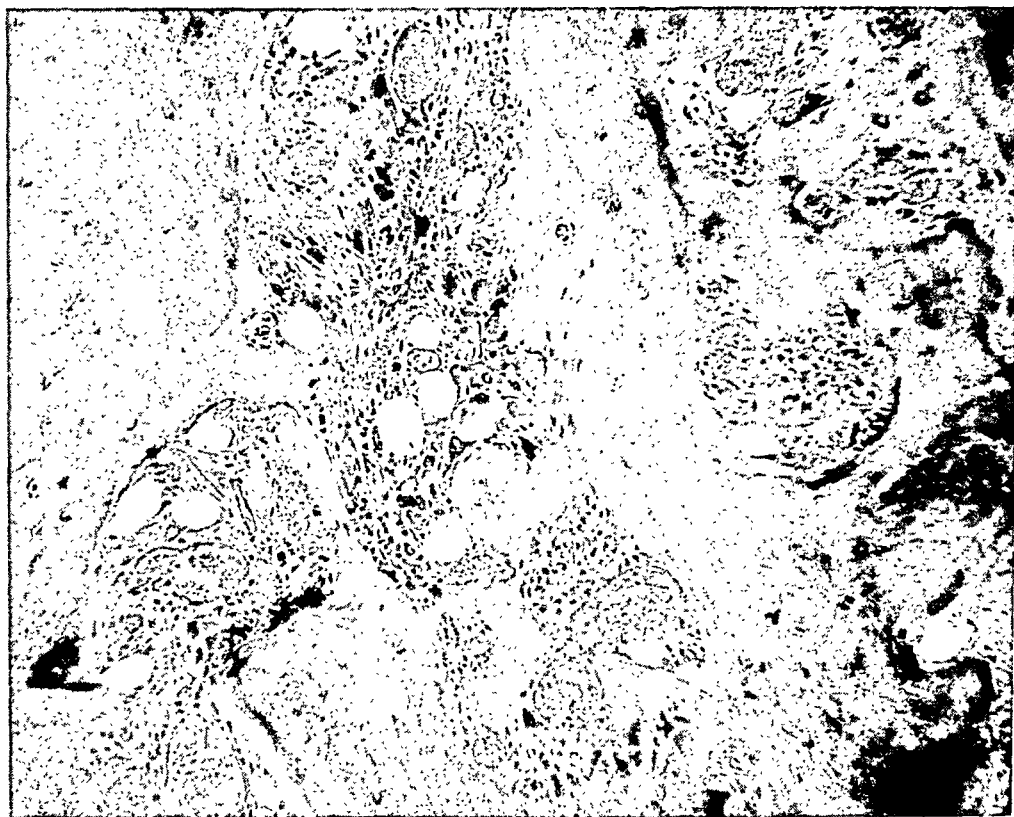


FIG. 4. Von Recklinghausen's disease; showing bone marrow replaced by neurofibromatous tissue.

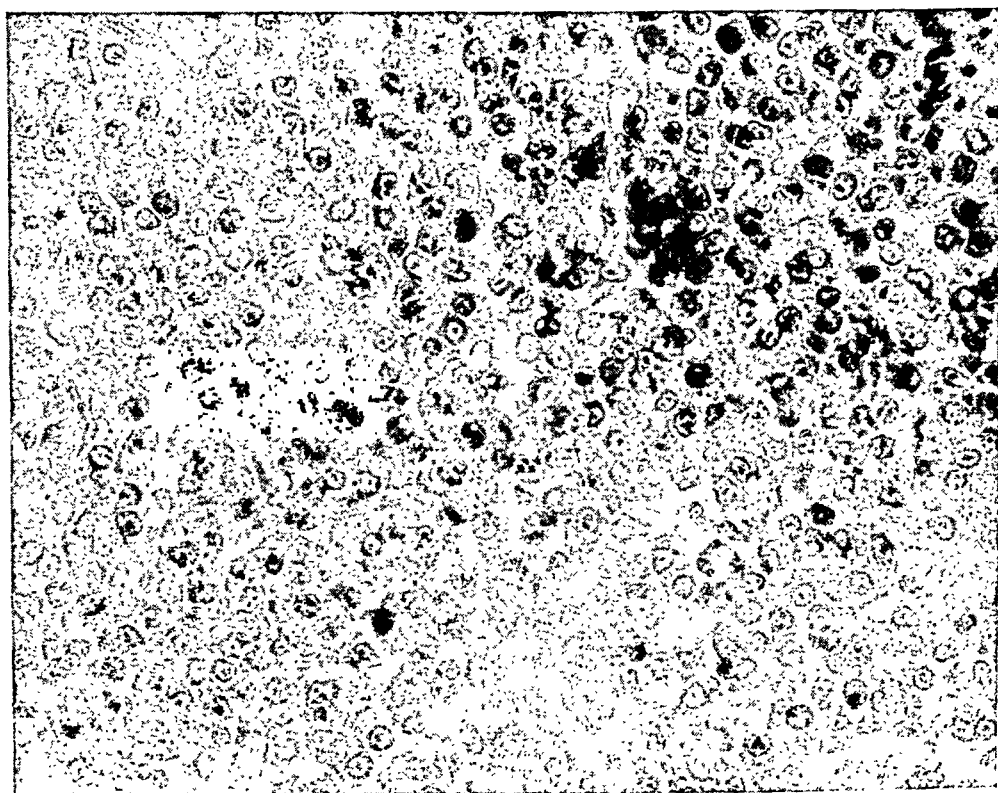


FIG. 5. Plasma cell replacement of bone marrow. Note almost complete absence of erythropoiesis.

had been in the hospital on three previous occasions and the following diagnoses had been made: (1) multiple neurofibromatosis; (2) dorsal kyphosis; (3) possible myeloid leukemia. He believed that he had injured his spine when he fell from a wagon at the age of three years. The deformity of the spine had been evident since the age of 14. He had had small, painless, papillomatous nodules in his skin since childhood. His symptoms at time of entry had started about one month previously and since then he had been dizzy almost constantly. He had noted double vision on occasions and several times had had a tendency to fall toward the right while walking.

*Physical Examination.* The patient was of short stature, poorly developed but fairly well nourished. Scattered over the body were seen innumerable non-tender nodules in the skin varying in size from 2 mm. to 2 cm. These were slightly elevated and a few of them were pedunculated. The thoracic vertebrae showed marked kyphoscoliosis and the chest was considerably deformed. The heart was displaced slightly upward and centrally. A soft systolic murmur was heard at the mitral area. The tip of the spleen was felt 6 cm. below the left costal margin and the edge of the liver was felt in the right epigastrium. A neurological examination revealed nystagmus on the right, a tendency to fall to the right, a positive Romberg and possibly motor weakness of the third nerve.

*Laboratory Data.* The blood count showed that between the years 1932 and 1936 the erythrocytes varied from as low as 2,780,000 per cubic millimeter to as high as 4,840,000 per cubic millimeter; the hemoglobin varied from 60 to 80 per cent (8.2 to 11 gm.) Sahli; and the leukocytes varied from 3,450 to 15,500 per cubic millimeter. The platelets were 180,000 per cubic millimeter. A typical differential count showed: segmented polymorphonuclear leukocytes 51 per cent; non-segmented leukocytes 21 per cent; polymorphonuclear eosinophiles 1 per cent; lymphocytes 6 per cent; monocytes 13 per cent; myelocytes 8 per cent. On numerous occasions from 1 to 4 normoblasts per 100 white blood cells were seen. The reticulocytes were 2.6 per cent. There were moderate poikilocytosis, anisocytosis, polychromatophilia and basophilic stippling of the red blood cells. The mean corpuscular volume was 66 cubic microns, the mean corpuscular hemoglobin was 22 micro-micrograms and the mean corpuscular hemoglobin concentration was 35 per cent.

Roentgenograms of the pelvis showed that the sacrum and both innominate bones had increased in density and contained areas of coarse trabeculation. In both femora were areas of decalcification and increased density producing an appearance of coarse trabeculation in the medullary canals. Similar areas were seen in the humeri. Conclusions: von Recklinghausen's neurofibromatosis of the bone marrow.

Biopsy of sternal marrow: The bone marrow was replaced almost entirely by tumor tissue. The cellular arrangement was moderately dense and the blood vessels contained in it stood out prominently on rounded structures surrounded by tumor tissue. The cells of the tumor tissue were markedly pleomorphic and hyperchromatic. Many of the cells were long, slender, undulating and arranged in wavy bundles, often with a fascicular or whorled appearance. Large dark multinuclear giant cells and mitotic figures were frequently seen. Diagnosis: neurofibroma of the sternum.

#### MULTIPLE MYELOMA (PLASMACYTOMA)

*Case 5.* J. P. S., a white American male, aged 53 years, entered the University of California Hospital on March 8, 1937, because of pain in his chest and epigastrium, weakness and loss of weight. His illness started three months prior to entry when he noticed weakness, generalized aches and malaise. Soon thereafter he became aware of pain high in the epigastrium and over the anterior and lateral parts of the chest. He described the pain as being sharp and sufficiently excruciating to inhibit cough and deep breathing. During the course of illness the pains became so generalized that

biopsy of the sternum. Specimens of marrow removed from the marrow cavity with a curette will show an altered architecture when properly fixed and sectioned. An attempt to remove representative tissue from the medullary cavity by the "puncture" method may prove disappointing. Hematopoietic cells may be obtained but the more compact neoplastic and sclerotic tissues will be retained by virtue of their desmoplastic reaction.

### CONCLUSIONS

A description is given of the hematologic aspects of space consuming lesions of the bone marrow. The group comprised 10 patients among whom were cases of myelosclerosis, osteosclerosis, neurofibromatosis, Gaucher's disease, carcinomatosis and multiple myeloma. The clinical findings were a moderately severe anemia, leukopenia, seldom an increased white count, and the presence of myelocytes and normoblasts in the stained films of blood.

The anemia is normochromic and normocytic. Myelophthitic anemia or disease of the blood formative tissue due to marrow replacement may be used as descriptive terms in the etiologic classification.

The similarity of the anemia in aleukemic myelosis to this type of anemia is discussed.

The value of examining the bone marrow by biopsy of the sternum in preference to the puncture method is emphasized.

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Case	Diagnosis	Hemoglobin		Red Blood Cells Millions per Cu. Mm.	Platelets per Cu. Mm.	White Blood Cells per Cu. Mm.	Poly-morpho-nuclear Leuko-cytes %		Basophiles, %	Eosinophiles, %	Lymphocytes, %	Monocytes, %	Myelocytes, %	Plasma Cells, %	Nucleated Erythrocytes per 100 Leukocytes	Mean Corpuscular Volume	Mean Corpuscular Hemo-globin Concentration %
		%	Gm				Segmented	Non-segmented									
1*	Osteosclerosis	44	61	2.26	205,000	14,100	61	19			15	3	2			97	21
2†	Myelosclerosis	43	6	2.08	10,000	4,200	20	18			15	4	43		3		
3†	Myelosclerosis	85	11.9	4.95	300,000	68,500	16	51		1	8	1	19		1		
4*	Gaucher's disease	58	8.1	3.64	90,000	1,300	38	23	1		23	10	4			79	29
5*	Carcinomatosis from breast	23	3.3	1.22	25,000	5,400	30	20		2	20	1	19		30	101	32
6	Carcinomatosis from breast	58	8.4	2.83	200,000	6,030	20	18	1	3	37	5	16		22		
7	Carcinomatosis from stomach	41	5.7	2.40	50,000	8,250	27	30		3	29		11		7		
8*	Neurofibromatosis	60	8.2	2.78	180,000	3,450	51	21		1	6	13	8		4	76	35
9*	Multiple myeloma	44	6.4	1.79	200,000	5,200	20	23	3	3	20	5	9	17	7		
10	Multiple myeloma	43	6.0	1.75	43,000	2,700	21	24	1	10	38	1	5		1		

\* Case history reported in text.

† See reference no. 4.

### BLOOD PICTURE

From the accompanying table it will be seen that at the time of examination anemia of variable degrees was present in 10 patients. The content of the blood was not altered by recent transfusions or treatment. The erythrocytes varied in number from a high level of 4,950,000 cells to as low as 1,200,000 cells per cubic millimeter. The anemia could be considered severe in one patient, of moderate degree in eight patients and of slight degree in one patient. The level of the hemoglobin was reduced in proportion to or slightly in excess of the erythrocytes, so that the color index ranged between 0.7 and 1.2. There was marked variation in the size and shape of the erythrocytes, and polychromatophilia or punctate basophilia were in evidence in all of the blood films. Nucleated red blood cells were noted in the stained films of nine of the patients; they varied from 1 to as high as 30 per 100 leukocytes.

Specimens of blood for the estimation of the volume of packed cells were obtained from five of the patients. It is to be noted in the accompanying table that the mean corpuscular volume was within normal range. The mean corpuscular concentration of hemoglobin showed normal or slightly reduced values. Accordingly the anemia could be classified as normocytic and normochromic.

In the cases reported here it is to be noted that with one exception neither the quantitative nor the qualitative changes typical of true leukemia were present in the leukocytic formula. The white cell count was reduced below 5000 cells per cubic millimeter in five of the patients, was within normal range in three and was greatly increased in two. A shift to the left in the granulocytes was shown by an increase in the non-segmented polymorpho-



In several previous papers I have discussed the features of "erythema multiforme" as observed in gonococcal bacteremia,<sup>2</sup> rheumatic fever,<sup>3</sup> and systemic lupus erythematosus.<sup>4</sup> In this communication it is my intention to describe the cutaneous and internal medical manifestations of what is probably a specific clinical entity—erythema multiforme exsudativum (Hebra). The data collected for this article are based chiefly on the personal observation of many isolated instances and several endemics of the disease. It may be put down as an axiom that when one example of this condition is seen many others are likely to be encountered at the same time.

### HISTORICAL DATA

Dermatologic analysis of the erythemas may be said to have begun with the work of Willan (1808)<sup>5</sup> and his pupil Bateman (1814).<sup>6</sup> Fundamental observations in morphology were contributed by Rayer (1835)<sup>7</sup> and Bazin (1862).<sup>8</sup> From the many varieties of eruptions classified in this category Hebra (1860)<sup>9</sup> differentiated a specific entity to which he gave the name erythema exsudativum multiforme. The importance of his endeavors lay primarily in the assembling of apparently diverse cutaneous lesions under one head and the recognition of the principle that they represented phases of a single condition. However, Hebra stressed morphology alone, and regarded the affection as essentially benign. Although Bazin<sup>8</sup> denied the unity of the several variants, he was the first to recognize the occurrence of lesions in the mouth and the prodromal constitutional symptoms in the vesiculo-bullous type of erythema multiforme exsudativum (hydroa vésiculeux); moreover, he clearly distinguished the herpes iris originally described by Bateman from the herpes circinatus (ringworm) attributable to fungus infection. Quinquaud (1882)<sup>10</sup> added an admirable account of the oral manifestations, while Kaposi,<sup>11</sup> Besnier and Doyen<sup>12</sup> and others emphasized the systemic features. In 1884 Leloir<sup>13</sup> furnished a masterly exposition of the pathologic anatomy of these eruptions. In the same year Duhring<sup>14</sup> segregated the clinical syndrome dermatitis herpetiformis. Even a part of pemphigus had to be salvaged from the inclusive category of erythema multiforme. Since then numerous dermatologists<sup>11, 15, 16, 17, 18</sup> and internists<sup>19, 20, 21, 22</sup> have concerned themselves with various phases of the subject, the opinions expressed being most diverse. In many cases futile debates arose because each observer was familiar only with his own special field. It is interesting, for example, to contrast the conception of the erythema group of skin diseases proposed by dermatologists<sup>23</sup> with that generally held by internists (Osler's erythema group).<sup>22, 24</sup> Throughout the history of these affections and even to the present time, the field has been dominated and obscured by vague notions regarding "arthritis," "rheumatism" and rheumatic fever. The major difficulty appeared to arise from certain resemblances in the clinical features presented by the various conditions. For example, there are at least six types of so-called erythema multiforme manifesting cutaneous lesions, joint pains, cardiac murmurs of functional or

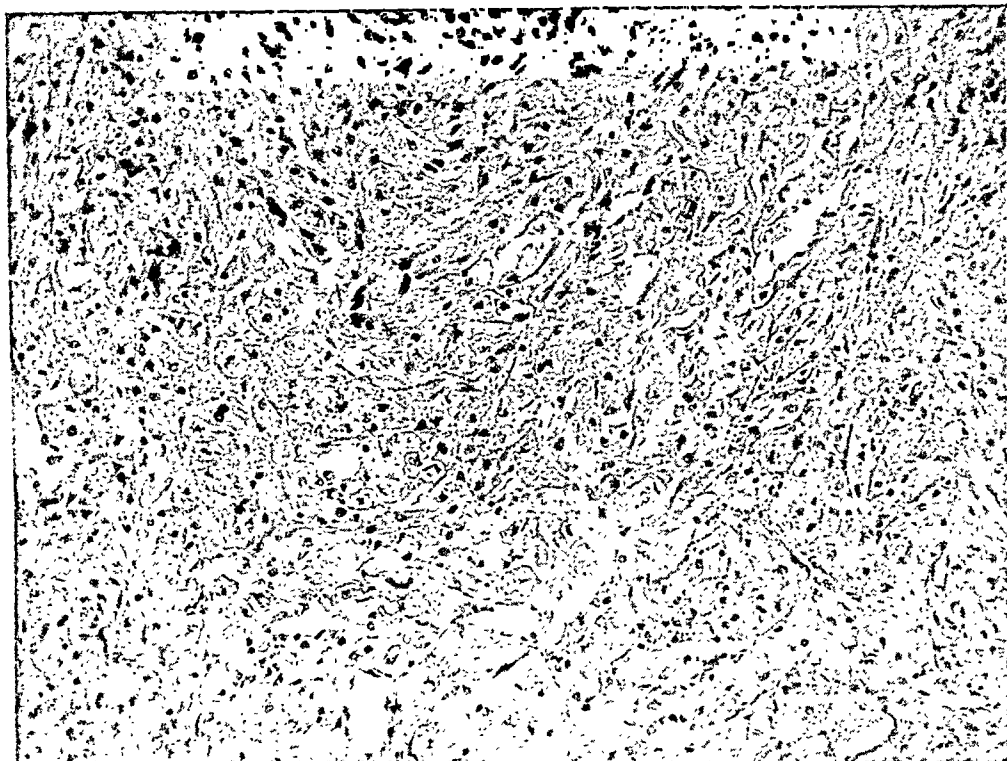


FIG. 2. Gaucher's disease showing kersin containing cells in the bone marrow.

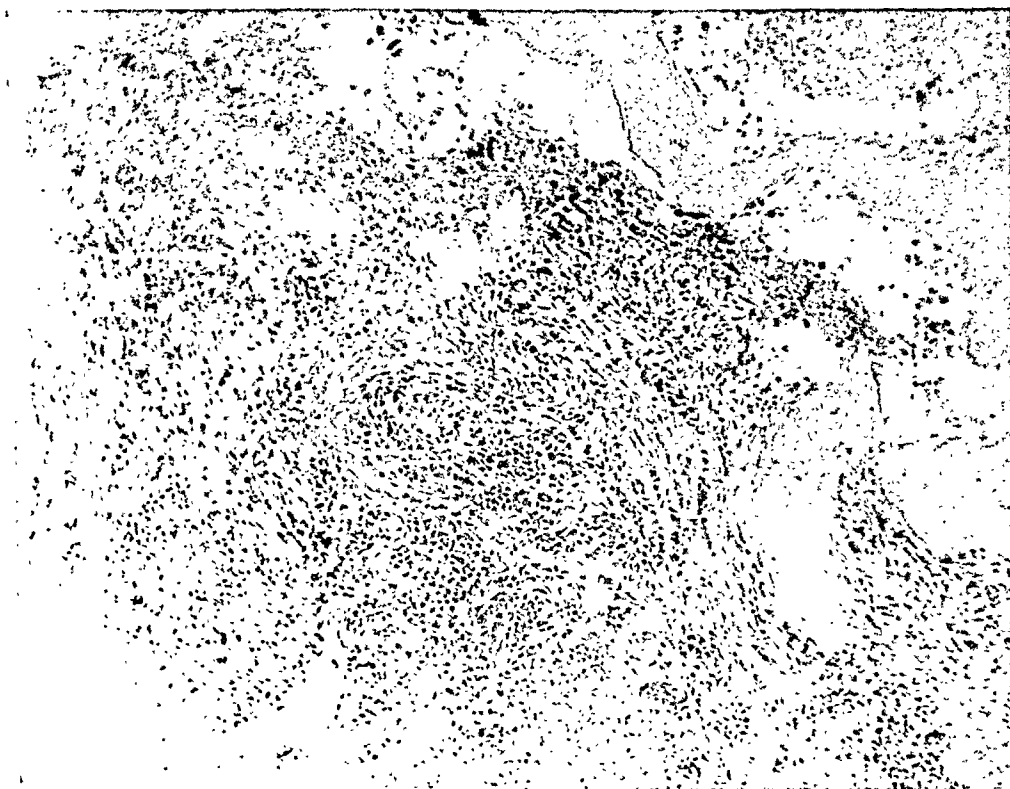


FIG. 3. Sternal bone marrow replaced by carcinomatous metastases from breast.

either in fresh crops or in subsequent recurrences of the condition. So far as polymorphous eruptions were concerned it was also noted that other diseases, such as dermatitis herpetiformis and acute lupus erythematosus, were often accompanied by lesions that were just as multiform in appearance as those in erythema multiforme exsudativum. It will be seen, then, that polymorphism cannot be used as an absolute criterion in the classification of disease. Despite this, the term erythema multiforme seems destined to be retained in nomenclature, its meaning being variously restricted or broadened.

### CLINICAL DATA

The cutaneous manifestations observed in erythema multiforme exsudativum may be conveniently classified in two groups, with numerous transitions: (1) erythemato-papular type; (2) vesiculo-bullous type. Both variants may be encountered in the same patient, either simultaneously or in subsequent crops or in later recurrences of the affection. The most striking features are: (*a*) the morphologic attributes of the cutaneous lesions; (*b*) definite predilection for certain parts of the body; (*c*) constitutional symptoms in a high percentage of cases; (*d*) a seasonal incidence in many instances and occurrence in endemics; when many cases are observed the impression of an epidemic may be created; (*e*) recurrences, especially during autumn and spring; (*f*) predominant incidence in young adults, though no age seems to be entirely spared.

The affection generally runs its course in from two to three weeks, but it may be prolonged one or two months, occasionally even longer. It is not uncommon to observe pigmented spots, the sequelae of healed lesions, for many months. Persistence of the disease is usually caused by the appearance of fresh crops of efflorescences, recurrent attacks of the systemic complaints, or the supervention of a complication, such as bronchopneumonia. The eruption is generally not chronic in the sense that individual lesions require a long time for involution. When, as in the rare examples of conjunctival and corneal involvement, residual changes remain visible or progressive in type, this is probably due to the nature of the affected structures and its potentialities for secondary infection, not to chronicity in the affection itself.

### CUTANEOUS LESIONS

1. *Erythemato-Papular Type.* The papular variety exhibits striking favor for the dorsa of the hands, this site being first affected, though by no means invariably. The eruption then extends symmetrically in one or more crops along the extensor aspects of the forearms, sides of the neck, lateral aspects of the face, and on the forehead. This manner of spread is of diagnostic import, especially when the lesions on the hands are not typical or when they are first seen in the process of involution. The dorsa of the feet and the extensor surfaces of the legs and knees are often involved, the lesions spreading upwards in crops, as in the case of the upper limbs. The palms,

The obviously active hematopoietic tissue was greatly reduced. Isolated groups of erythropoietic or myelopoietic cells could be seen between strands of connective tissue or among the tumor cells. Although the pathologic process varied in the different cases, the findings of a few myeloblasts, comparatively large numbers of myelocytes and a few segmented cells seemed to be common to all. Normoblasts and a few erythroblasts represented erythropoiesis. The replacement of the marrow by the sclerosing or infiltrating processes and the altered anatomic arrangement of the marrow cells, it is believed, could account for the hematologic picture of anemia, normoblastosis, leukopenia and a shift to the left in the leukocytic formula.

### DISCUSSION

In the 10 patients whose hematologic data are presented here space consuming lesions of the bone marrow were found. Following biopsy of the sternum the diagnoses were: myelosclerosis in two patients, osteosclerosis in one patient, neurofibromatosis in one patient, Gaucher's disease in one patient, carcinomatosis in three patients, and multiple myeloma in two patients. The anemia was characterized by moderate severity and was of a normocytic-normochromic type. Since the abnormal tissue caused mechanical alteration of the marrow, the anemia could be designated in the etiologic classification as myelophthysic or simply as disease of the blood formative tissue due to marrow replacement. Normoblastosis and myelocytosis were observed in all the stained films of blood. The cases were reported because of their rarity and because of the difficulties encountered in making a differential diagnosis from aplastic anemia or aleukemic myelosis.

Aplastic anemia can usually be differentiated from myelophthysic anemia by the lack of signs of regeneration of the red blood cells in the former. Rhoades<sup>7</sup> recently promulgated the idea that some cases of sclerosis of the bone marrow should be classified as sub-groups of aplastic anemia. The basic defect he believed could be attributed to an arrest of maturation of erythropoiesis as a result of replacement of hematopoietic cells and associated with an absence of immature cells in the blood.

In the cases reported the resemblance of the hematologic findings to aleukemic myelosis is striking. In a recent study of this disease<sup>8, 9</sup> it was observed that normoblastosis was a constant finding. The anemia was normocytic and normochromic. A difference noted in the differential formula, however, was a shift to the left to include not only myelocytes but also myeloblasts. This close similarity of the anemia in this group to that in patients with sclerosis of the marrow suggests that abnormal erythropoiesis may be an arrest of maturation induced by the deranged anatomical structure of the marrow.

It must be emphasized that the diagnosis of the unusual type of anemia presented here may be suggested by the myelocytic-normoblastic reaction, substantiated by the roentgen films of the bones and usually confirmed by

Involvement of the mucous membranes and the occurrence of constitutional symptoms may accompany the papular type of erythema multiforme exsudativum. However, these manifestations are usually seen less often and are generally less pronounced than in the case of the vesiculo-bullous variety and may, indeed, be altogether wanting. This rule, however, admits of many exceptions. One of the most important of these concerns the cases characterized by profuse papular lesions found on the trunk; apparently this type is accompanied by systemic reactions in a large proportion of instances, and its occurrence may be regarded as evidence of increased severity in the disease. The few cases grouped under the title of Stevens-Johnson syndrome<sup>29</sup> appear to fall in this category. The lesions in the mucous membranes and the constitutional symptoms will be discussed in greater detail in later sections of this article.

*2. Vesiculo-Bullous Type.* This variety is often seen by internists, pediatricians and ophthalmologists. Numerous examples have been recorded under diverse titles and a prolific patronymic nomenclature has arisen. Of historical interest was the polemic between Gerhardt<sup>20</sup> and Kaposi<sup>11</sup> relative to the classification of this disease, the controversy having concerned the status of cases originally recorded by Wunderlich<sup>19</sup> as "phlyctenular fever." The more recent literature also contains opinions reflecting significant differences in conception.<sup>29, 30, 31, 32, 33, 34</sup> The group of cases reported by Meyer,<sup>35</sup> for example, under the title of "acute articular rheumatism with erythema pustulosum" were probable instances of vesiculo-bullous erythema multiforme exsudativum accompanied by secondary clouding of vesicles, rather than examples of genuine rheumatic fever. It may be stated, parenthetically, that the cutaneous lesions in rheumatic fever rarely, if ever, show a vesicular, bullous or pustular component, and that in the excessively uncommon instances where such phenomena have been described the diagnosis was doubtful.<sup>3</sup>

In general, the eruptions considered in this section are the counterpart of papular erythema multiforme exsudativum, except that exudation of fluid and cells is so intense as to result in the formation of vesicles and bullae, usually centrally disposed. It is common to observe a vesicle or small bulla capping the centers of papular lesions. The name herpes iris is generally applied either to those efflorescences revealing the appearance just described or to configurations of vesicles or bullae arranged concentrically. As in the case of erythema iris, these lesions or variants of them arise from repeated local central recurrences, with or without peripheral spread of each fresh focus and, similarly, there may be a play of colors from the center to the periphery. The occurrence of pustules is attributable either to clouding of vesicles or superimposed infection and, as such, represents a secondary rather than a primary element in the eruption.

#### FEATURES OF SPECIAL INTEREST

Before describing the less characteristic lesions in the mucous membranes it appears desirable to analyze a number of special features. The recog-

## ERYTHEMA MULTIFORME EXSUDATIVUM (HEBRA); A CLINICAL ENTITY ASSOCI- ATED WITH SYSTEMIC FEATURES \*

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CUTANEOUS lesions labeled as erythema multiforme are often encountered in medical practice. Variations in clinical course, a complicated nomenclature, and the artificial hiatus separating dermatology from internal medicine have been contributory factors in making a difficult subject even more involved. The literature is replete with controversies regarding the conception of erythema multiforme and the so-called erythema group of skin diseases. Though from time to time well-defined entities have been differentiated from this all-inclusive category, the concept of erythema multiforme, as described in the average American textbook on dermatology, still comprises a multitude of heterogeneous eruptions. It is true that the skin may react to the same morbid agent in a variety of ways (Besnier's dictum), and it is also certain that there are abundant transitions between well-characterized conditions (Brocq's *réactions cutanées*), creating difficulties in the differential diagnosis. Yet, study of dermatoses in terms of the internal medical manifestations will often reveal features or combinations of features that permit accurate classification.<sup>1</sup> This principle has hardly received the consideration it deserves.

The diagnosis of erythema multiforme or multiform erythema (toxic erythema) may be regarded as purely descriptive. In truth, it affords no clear insight into the nature of the general underlying process, and, what is also important, it adds little information about classification and still less about prognosis. Already there are manifest signs of a trend that decries the descriptive method, but this view is based on the supposition that morphology has reached its peak and exhausted its possibilities. This belief is, however, only a half-truth, and nothing illustrates the point better than a study of the eruptions comprised within the category of erythema multiforme. The time appears to be ripe to attempt a subdivision of this *caput mortuum* into a number of entities. In the average case these conditions may be separated from one another with comparative facility, if studied in terms of the composite clinical picture and in the light of instances seen not only in private practice and dispensaries, but also in the medical wards. These differentiations are essential to the proper grouping of cases for further investigation; moreover, methods of treatment may be employed rationally and a more accurate prognosis formulated. However, there may be difficulties in diagnosis owing to the occurrence of what seem to be transitional instances, and these cases should be placed to one side for subsequent study.

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Dr. Harry A. Solomon, the hands, which had been the site of closely apposed bullae, revealed as an aftermath the appearance of large epidermal lamellae, with exposure of the underlying bright-red smooth epidermis. Phenomena of a similar order have been encountered by other observers.<sup>41, 42, 43</sup>

It will be seen, then, that the occurrence of desquamation of this type, in the presence or apparent absence of obvious exudative lesions, affords no basis for the belief that the clinical picture is distinct from erythema multiforme exsudativum.

5. *Pigmentation and Depigmentation.* Areas colored various shades of brown are often left in the wake of this eruption, and these may remain visible for weeks, occasionally for many months.<sup>44, 45</sup> It is to be emphasized that this occurrence is noted as a sequela, rather than as an accompaniment of the early stages in the lesions. It seems likely that the phenomenon is due, at least in part, to a degree of microscopic hemorrhage.<sup>13, 12</sup> There are, however, many instances in which pigmentation remains visible for so long a time as to awaken the belief that this is not entirely dependent on microscopic extravasations of blood; it appears probable that in such cases there is a secondary "inflammatory melanosis" similar to that encountered in drug eruptions, for example, those due to phenolphthalein.<sup>47, 48</sup> This I was able to substantiate in at least one patient from whom biopsy specimens were taken in the stage of involution, but it is a matter easily resolved by more extensive minute anatomical studies. The brown spots may be so widely distributed as to create a speckled appearance, but they are not accompanied by any degree of atrophy.

Rarely the lesions may fade, with the production of depigmented areas at the sites (leucoderma); this unusual sequela occurs variably even in the same patient, for it may be present in one attack, absent in others.<sup>50</sup>

6. *Atrophy, Ulceration and Scarring.* Atrophy secondary to pathologic alterations in the cutis is not observed in this affection, nor have I met with thinning of the epidermis in authentic examples of the disease. This interesting point merits notice, for in the superficial types of "systemic" lupus erythematosus the edematous fluid appears to possess different properties, resulting in atrophy or at least marked thinning of the epidermis.<sup>4</sup>

For various reasons to be mentioned later lesions in the mucous membranes often assume the form of erosions, but it is common to observe complete healing, and the production of cicatrices is rare; this affords evidence that the pathologic process is essentially superficial. My own observations are in agreement with those who deny the occurrence of ulceration as a fundamental method of healing in erythema multiforme exsudativum.<sup>49</sup> When ulceration occurs, especially in the mucous membranes, it represents probably the effect of secondary infection or of drastic treatment; this complication is seen more commonly in the mucous membranes, rarely in the skin, and is followed by scarring incident to granulation tissue.

7. *Hemorrhagic and Aberrant Bullae.* That bullae occur in erythema multiforme exsudativum is well established. It has also been observed, as in

organic origin, fever, and even prodromal sore throat; yet study of the composite clinical picture and of the attributes shown by the eruptions reveals significant differences in a high percentage of cases. It is possible to recognize the nature of the "erythema multiforme" in most of the instances recorded in the older literature, though the titles under which they were described were often vague and sometimes erroneous.

In its principal outlines the conception of this disease as an entity seems to be accepted by many European dermatologists.<sup>25, 26, 27</sup> Indeed, this is the only type regarded as meriting the title erythema multiforme or erythème polymorphe, all other simulating eruptions being classified in the category of "symptomatic polymorphous erythemas" or "toxic erythema." For the most part American dermatologists<sup>46</sup> tend to deny the authenticity of Hebra's erythema multiforme exsudativum, a notable exception being Klauder.<sup>28</sup> My own observations appear to support the belief that this disease is a specific entity; that, at least in New York City and its environs, it is not rare during the spring and autumn months; but that it is usually labeled with a variety of names, of which the most common is "toxic erythema."

#### DEFINITIONS

In its broadest sense the term erythema multiforme is used to designate erythemato-papular rashes of relatively acute onset and brief course, showing special favor for the extensor aspects of the limbs; this holds especially in the case of eruptions that cannot be classified precisely.\* In many instances there may be added a vesicular, pustular or bullous component, but these elements are facultative. Realizing that this descriptive basis for classification has shortcomings, some have employed the name "multiform erythema" in a comprehensive sense similar to that enjoyed by the generic term polymorphous erythemas. Recent reports in the French literature<sup>26</sup> indicate that an attempt is being made to restrict the designation erythème polymorphe to the specific entity described by Hebra. It is probable that the term "multiform erythema," often used expediently, will be applied less frequently as specific conditions are segregated from this heterogeneous group.

The qualifying word "multiform" requires explanation. It was probably first introduced by Hebra for the purpose of indicating the close relation existing between several dermatologic lesions that had been previously classified in separate categories; for example, erythema papulatum, erythema marginatum, erythema tuberculatum, herpes iris, etc., etc. It was, however, soon recognized that at any given moment the lesions might be of a single type; under such circumstances the eruption hardly merited its full descriptive title. On the other hand, continued observation in many such cases revealed polymorphism arising from (1) variations in the development of individual lesions, and (2) the introduction of new types of efflorescences,

\* For example, Kaposi included lichen urticatus which is now recognized as a separate entity, allied to urticaria (papular urticaria).



observation it became certain that this patient did not suffer from erythema multiforme exsudativum, though the precise nature of the malady was still obscure.

*9. Relapses and Recurrences.* Relapses in this affection are common. It is probable that exceptional instances featured by a prolonged course,<sup>12, 56</sup> measured in months or years, may be explained on the basis of this factor, though in some cases the distinction between a relapse and a recurrence was not always easy to determine. Aside from complications and sequelae the individual efflorescences in erythema multiforme exsudativum evolve in a relatively short time, contrasting, for example, with the chronicity displayed by the average lesion in pemphigus.

If cases of this disease are observed over many years and careful histories taken, it will be found undoubtedly that recurrences are relatively common. This feature is more often exhibited by the vesiculo-bullous form, but I have also met with it in several cases showing erythemato-papular rashes. Jordan<sup>57</sup> has roughly estimated the incidence of recurrences as 17 per cent, and the literature abounds with examples illustrating this fundamental point.<sup>8, 9, 12, 45</sup> Accurate statistics are, however, not available as yet. In addition, Hebra described an annual recurrent type, and it is not rare to observe repeated attacks at certain seasons, especially autumn and spring,<sup>12, 58, 45</sup> though there is often great variability in this respect.

In many instances the same type of eruption recurs. I must, however, agree with those who have noted variations not only in regard to morphologic attributes, but also in regard to location of lesions.

*10. Endemics and Epidemics.* It has been stated that the observation of one case generally means that more patients of this sort will be seen shortly. This is explained, in large measure, by the factor of seasonal incidence (spring and autumn), though isolated instances may be encountered throughout the year. The occurrence of this disease in minor or major epidemic proportions has been recorded by many writers.<sup>51, 55, 58, 59, 60, 61</sup> In most instances these epidemics concerned soldiers who were quartered in the same barracks or nearby. It is, however, more common to encounter the affection in endemic form, especially at the favored seasons, as I have observed several times. The disease is occasionally met with in several members of a family, but on the whole this is an uncommon occurrence. In a few instances other patients in the same medical ward have been found to become affected by this condition. There is, however, no definite evidence that erythema multiforme exsudativum is a contagious disease, directly transmitted from one person to another.

*11. Alliance Between the Papular and Vesiculo-Bullous Forms.* Although Hebra discussed herpes iris and its variants under the general category of Herpes, he presented cogent reasons for allying these lesions with the papular form. To summarize: (a) both types may appear in the same person, either simultaneously or subsequently; (b) they show similar sites of predilection and their clinical course is fundamentally alike; (c) recur-

soles, arms, thighs, inner aspects of the perineum, back of the neck near the scalp line, and the trunk are other areas occasionally affected, but no portion of the body is spared, with the possible exception of the scalp proper. Even the latter part of this rule may have exceptions, though I have not met with them. The incidence with which the various areas are involved differs with individual accounts, but this is of no great moment, as the eruption exhibits a characteristic pattern in most cases. The average duration of each crop is from six to 10 days, but lesions situated on the face and lobes of the ears appear to undergo more rapid involution, roughly in from three to five days in the instances under my observation.

The primary element is an erythematous macule that speedily becomes elevated (papule), owing to the increased intensity in the exudative phenomena (edema and perivascular infiltration). When there is pronounced exudation of fluid the elevation shows attributes resembling ordinary urticaria (urticarial component). The center of the papule generally acquires a characteristic peculiar violaceous hue, attributable to tremendous congestion and stagnation of blood in the vessels occupying the upper and middle portions of the cutis. As the lesion spreads peripherally the central portion becomes relatively depressed and cyanosed, whereas the advancing border is raised above the level of the skin in a bright red fringe. In occasional instances, as in two cases under my observation, this characteristic evolution was abortive, and the papules showed a peculiar brownish red hue; under such circumstances recognition of the eruption becomes more difficult and the diagnosis must perforce be based on the manner of spread and the general features of the affection.

In other cases there is centrifugal extension of the borders. Coalescence of contiguous lesions results in the formation of margined figures of various sizes, shapes and complexities, the enclosed areas being discolored. In its morphologic attributes this variant resembles erythema marginatum rheumaticum, the differential features of which will be summarized in another section of the article.

Thus far I have described the simple papular efflorescence and its manner of evolution. A more characteristic appearance illustrating the essential nature of the process is that furnished by the so-called erythema iris and its variants. This name has been applied to various lesions, but the fundamental principle is that within a short time, generally measured in days, there occurs resumption of activity in the centers of efflorescences, with or without subsequent peripheral spread of the recent focus. Thus, the centers may show a fresh bright-red papule, vesicle or bulla, or there may be concentric rings of various hues, creating an iridescent pattern owing to the differences in the stages of evolution from center to periphery. This process may repeat itself several times, with the production of complicated iris figures showing an astonishing play of colors; in principle, however, these lesions merely represent examples of erythema papulatum characterized by central relapses, with or without evidence of subsequent centrifugal spread.

bluish hue due to extravasation of blood in excess of what is to be normally expected.<sup>45</sup> It has been claimed that necrosis of cutaneous lesions, analogous to that seen in the gastrointestinal tract, is often encountered, but my observations appear not to substantiate this belief, though the post-mortem examinations in many such instances revealed a fair incidence of superficial necrotic areas along the gastrointestinal tract. The one exception was a case of hemorrhagic gangrenous herpes zoster of the trunk occurring in a patient dying in uremia, but, as the former may reach a similar degree of intensity under ordinary circumstances, it was difficult to assess the importance of the phenomenon. However, it seems likely that hemorrhage of pronounced degree, as is often observed in the cutaneous lesions in uremia, may be accompanied secondarily by disintegration of tissue. In another section of this paper the relation between erythema multiforme exsudativum and nephritis will receive further consideration.

13. *Isomorph Reizeffekt*. Under the term Köbner's phenomenon dermatologists have long recognized that normal areas of skin in patients with psoriasis will often reproduce the primary lesions of that disease when subjected to various types of trauma. It was later found that a few other affections, of which lichen planus is a conspicuous example, may exhibit this behavior, and this property is sometimes utilized in the form of a test in obscure cases. Kreibich,<sup>65</sup> who has actively concerned himself with this "isomorph reizeffekt," observed it in several classical examples of vesiculobullous erythema multiforme exsudativum as well as in erythema nodosum; this phenomenon he was able to demonstrate with the use of such various agents as trichophytin, isotonic saline solution, sterile distilled water, scratching the skin or excoriating it with a needle. Kogoj<sup>66</sup> has apparently substantiated, in principle, the observations of Kreibich in erythema multiforme exsudativum, and has further shown that the results obtained by such traumas depend often on the time the experiment is conducted. This phenomenon is important in evaluating the significance of the agents that have been or will be used in an effort to trace the etiology of this and other affections, for example, the employment of streptococcal extracts, tuberculin, trichophytin, etc. In all cases it will be essential, by means of appropriate controls, to differentiate a specific reaction from the non-specific "isomorph reizeffekt."

#### LESIONS IN THE MUCOUS MEMBRANES

Involvement of the mucous membranes is an integral part of the disease erythema multiforme exsudativum. Its incidence has been variously estimated at from 25 per cent to approximately 60 per cent; the former figure appears to be more nearly accurate. It may be laid down as a general rule that, with but few exceptions, the dangers and the prognosis of this affection are proportionate to the severity of these manifestations. In the ordinary papular type the mucous membranes are generally spared, but there are many exceptions; it is essential, therefore, to examine these parts in every patient,

nition of these points is essential in understanding the protein disease erythema multiforme exsudativum.

1. *Age and Sex.* Though the affection is encountered most commonly in young adults of both sexes, it may occur at any age, including the extremes. Schlesinger<sup>36</sup> observed that the disease may be more severe in the average example of erythema multiforme exsudativum seen in children, but this rule, though valuable, is not without exceptions.

2. *Subjective Symptoms.* As a rule the eruption runs its course, without the occurrence of striking subjective complaints, aside from a trifling sense of burning in some cases; at times there may be a degree of pruritus, but this is rarely intense. This rule is, however, violated in many patients presenting lesions in the mucous membranes, as will be noted later.

3. *Influence of Location.* The morphologic attributes may be considerably modified or influenced by location. Thus, lesions in the soles and palms tend to remain macular, owing to the unyielding thick epidermis in these situations. Efflorescences appearing on the lower limbs may become nodular, somewhat painful, and assume a bluish hue, with decided resemblances to erythema nodosum<sup>12, 27, 37, 38, 40</sup>; these modifications are often exhibited by many dermatoses affecting the lower extremities,<sup>39</sup> and they are correlated best with the nature of the involved tissue (poor circulation) and the probable occurrence of pathologic alterations in the deeper parts of the cutis and the adjacent areas. Lesions situated in the mucous membranes are modified profoundly for reasons that will be noted in another section of the article.

Edematous infiltrations are occasionally encountered in various parts of the body, and they may arise from a variety of causes: (*a*) the tissue may be of loose texture (eyelids, prepuce, labia majora, lips, etc.); (*b*) the exudation of edematous fluid may be especially intense or may be favored by anatomical relations (dependent parts, etc.); for example, there may be localized swellings in the face, tongue, hands and legs. I have seen on several occasions the dorsa of the hands so markedly swollen as to interfere with closing of the fists. This attribute, though usually of brief duration, is not to be confused with angioneurotic edema or true urticaria.

4. *Scaling, Crusting and Desquamation.* The simple papular efflorescences in erythema multiforme exsudativum may be attended occasionally by slight scaling, but these scales appear not to show the adherent qualities or the "carpet-tack" appearance seen in lupus erythematosus. In some cases this phenomenon may be attributed to the presence of vesicles that are generally visible, sometimes inconspicuous and ephemeral. Crusts may be formed consecutive to the rupture of vesicles or bullae, but it is also possible for these to resorb completely, without leaving any sequelae. The occurrence of rapid absorption or drying of lesions produces the appearance of scales, rather than crusts; under such circumstances a widespread bullous eruption may be succeeded by what is popularly interpreted as ordinary desquamation. In a case recently observed by me, through the kindness of

but it appears that cicatrization represents not an inherent method of cure, but rather the result of secondary infection and ulceration.

The favorite sites of the enanthem are the buccal mucosa, vermillion of the lips, and the hard and soft palates, but other areas may also be affected. In one case under my observation there occurred almost complete ulceration of the uvula, a probable sequel to secondary infection. The process extends occasionally to the pharynx, larynx, tracheobronchial tract and, rarely, to the esophagus; it is the involvement of these parts that accounts for a large proportion of the lethal complications, as will be described later.

Subjective symptoms may be absent or mild in many instances, but there are examples featured by especially severe complaints. A complete description of these manifestations will be deferred until the internal medical features of this affection are considered, for they merge imperceptibly.

The average appearance of lesions at the height of development, then, is that of a superficial erosion covered usually by a whitish membrane and surrounded by a peripheral dark red or violaceous red zone several millimeters wide. Sometimes the central deposits are yellowish or distinctly hemorrhagic. The overlying membrane is usually soft and pulpy in consistency, and, when wiped away with a cotton plug, leaves bleeding areas. Other variations in appearance seem to be determined in large part by the location of the enanthem. There are instances in which only a diffuse redness of the mucous membranes is found; on the other hand, pure erythematous isolated lesions, without manifest evidence of exudation, are generally observed on the hard and sometimes the soft palate, this being attributed to the firm adherence of the mucous membrane in this situation to the underlying parts. In areas showing similar anatomical relations (pharynx, gums, vocal cords, etc.)<sup>94</sup> the pathologic alterations may assume the form of more solid elevations; papules, nodules and irregular tumor-like infiltrations. The hemorrhagic element is especially marked in lesions situated on the lips; it is common to find, as a result of the rupture of bullae, fragile crusts that often bleed on the slightest trauma.

It will be seen, then, that the characteristic cyanosed centers observed in the cutaneous lesions are apparently lacking in the enanthem. The latter also shows a greater tendency to form coalescent areas; this holds particularly in the case of the lips where one or more confluent patches may cover these parts. Annular figures and iris-formations are rarely encountered; when present, they are probably pathognomonic of erythema multiforme exsudativum.<sup>49</sup>

It is the rule for complete healing of the enanthem to occur, but relapses are common. There is also a marked tendency to recur, and instances illustrating several attacks in the mouth are common. It has been claimed that lesions may recur in the same areas and that local thickenings in the mucous membrane at these sites may result therefrom. This I have not yet had the opportunity of observing, but other writers have described this occurrence in what appear to be representative examples of erythema multiforme ex-

several cases seen by me, that isolated lesions of this sort may occasionally appear without the usual erythematous halo.<sup>12, 13, 44</sup> This may result in decided resemblances to pemphigus, but, as stressed by Besnier, the diagnosis must be based on the totality of the eruption, rather than on a few isolated efflorescences.

Opinions differ, also, relative to the appearance of gross hemorrhage within bullae. Thus, Tachau,<sup>27</sup> who accepted the occurrence of microscopic extravasations of blood, denied the authenticity of cases of erythema multiforme exsudativum showing this phenomenon clinically. It seems true that many such recorded instances were lacking in essential particulars or were described under erroneous titles (examples of gonococcal erythema multiforme,<sup>2</sup> Osler's erythema group,<sup>1</sup> systemic lupus erythematosus, drug eruptions, etc.). Despite this, my own observations appear to support the belief that hemorrhagic bullae may occur occasionally, and similar findings have been noted by others in authentic cases of this disease.<sup>37, 44, 52, 53, 54, 55</sup> Two general features exhibited by this group of cases have caused hesitation in accepting this phenomenon as part of the affection: (1) the widespread distribution of the lesions, rendering difficult the recognition of the ordinary attributes of erythema multiforme exsudativum, especially in cases seen early in the course; (2) the common association with instances featured by severe constitutional symptoms. Intimately involved in this polemic is the status of the so-called Stevens-Johnson disease,<sup>20, 84</sup> which will be discussed in the section on the conjunctival and corneal changes seen in Hebra's erythema multiforme exsudativum.

8. *Miscellaneous Atypical Features.* In studying this disease there have come under my observation cases that were more difficult to recognize on account of the following features: (*a*) the eruption was restricted to a single or two crops in all, and the lesions were sparsely distributed; (*b*) the dorsa of the hands, a favorite site, were entirely spared or were affected relatively late in the course; (*c*) the eruption, rarely, showed a tendency to affect the flexor surfaces; when restricted to these areas, the condition has been called the "inverse" type, but similar atypical features may be exhibited by many other cutaneous affections; (*d*) occasionally lesions appeared on the "flush area" of the face and these by coalescence formed a more or less diffuse erythema simulating superficial lupus erythematosus, but these patches were characteristically transient; (*e*) the lobes of the ears were affected occasionally, a feature observed more commonly by Leipner<sup>51</sup> who met with it in 12 out of 30 cases; however, unless the eruption is transient, the possibility of lupus erythematosus or other dermatoses should be borne in mind. In the early stages the differentiation may be difficult, and I have seen a number of examples of lupus erythematosus in which the incipient lesions were diagnosed as erythema multiforme exsudativum, though the eruption did not present the typical features of the latter dermatosis. In one case, for example, the condition was regarded as hemorrhagic bullous erythema multiforme, with conspicuous involvement of the ears; after several years of

out alterations in other mucous membranes. The prognosis for complete recovery was, therefore, regarded as excellent.

Simultaneously, however, severe examples of conjunctival and corneal involvement were observed, chiefly by the ophthalmologists who were consulted for these complications, occasionally by the pediatrician because many of the patients were children, and sometimes by the internist owing to the constitutional symptoms. In this manner, a rich literature containing abundant protocols was recorded, but the subject, instead of being simplified, became more complex, for now there were added a few new diseases and some patronymic titles. It is my intention to discuss these cases which appear to differ from erythema multiforme exsudativum and to attempt to show that they represent variants of this protean affection.

In discussing the problem it will be advantageous to begin, first, with a consideration of the milder examples and, then to lead, by a series of gradual transitions, into those instances presenting clinical pictures more difficult to classify.

*a. Mild Cases.* These manifest signs of a superficial "catarrhal" process. The eyelids are normal or moderately edematous. The palpebral conjunctivae are hyperemic and slightly hypertrophied; in more prolonged cases the bulbar portion is injected, glassy, and swollen with edematous fluid. There is increased secretion from the eyes, usually of a serous type, more uncommonly mucoid. In several examples under my observation the lids were pasted to the adjacent parts owing to the occurrence of a mucoid or mucopurulent secretion. Subjective symptoms are inconspicuous; at the most there may be smarting sensations and distress from the accumulation of exudative material. The course has a duration of from one to several weeks or longer. Healing occurs in the absence of important sequelae. Illustrative examples have been recorded in the older literature by Hanke,<sup>73</sup> Neumann<sup>74</sup> and Bergmeister<sup>75</sup> among others. In these cases the cutaneous manifestations were typical of vesiculobullous erythema multiforme exsudativum. In the first two instances cited, there were, in addition, characteristic lesions in the oral mucous membranes. Bergmeister's case is of particular interest owing to the many recurrences in the conjunctiva, absence of febrile reaction, and the occasional appearance of lesions in the eyes in advance of the exanthem. The more recent literature contains a number of examples showing somewhat more pronounced conjunctival lesions<sup>54, 67, 70, 76</sup>; of these the case recorded by Blair<sup>54</sup> merits particular interest, as it concerned a boy aged 12, in whom there were observed six separate attacks of the disease, with involvement of various parts of the integument. Related to this group are the numerous instances described by many other investigators under a variety of titles; these will be mentioned again in the section concerned with the lesions encountered in the miscellaneous mucous membranes.

*b. Severe Cases.* These take the form of "membranous or pseudomembranous conjunctivitis," affecting chiefly the palpebral portions and accom-

rences are observed in both types and these manifest the same seasonal incidence. The data recorded in the literature and in this paper appear to substantiate amply this fundamental relation.<sup>27, 45, 58, 62, 63</sup>

*12. Coincidental and Concomitant Disease.* The evaluation of the factor of coincidence in diseases and the possible influence of one affection upon another has always been a delicate problem. There is no evidence indicating that erythema multiforme exsudativum confers an immunity against any other condition. There is still less ground for denying the occasional close similarities in clinical picture between erythema multiforme exsudativum and a host of simulating diseases, as will be noted in discussing the differential diagnosis. There is, however, one affection requiring brief mention at this time, namely, "nephritis." This has been regarded by some as a frequent concomitant of erythema multiforme exsudativum, but, in agreement with the opinion expressed by Tachau, I am unable to substantiate this relation.

In analyzing closely the older reports, it appears that the following criticisms are justified: (a) the criteria for the diagnosis of "nephritis" were often inadequate; (b) no systematic effort was made to differentiate the various types of renal involvement, and but few reports contain adequate minute anatomical data; (c) there are many recorded instances showing disease in the kidneys, but, as stressed by Tachau, the diagnosis of the eruption was often erroneous; (d) the factor of coincidence was not taken into consideration. There are undoubtedly a few recorded cases exhibiting the combination of true inflammatory nephritis with renal failure and erythema multiforme exsudativum or an eruption simulating it. In 1932 Chargin and I<sup>64</sup> analyzed the data found in 1100 records of various types of renal disease in respect to the dermatoses encountered. Since then many additional rashes of this sort have come under my observation, and it appears that the problem is chiefly concerned with cutaneous lesions occurring in the period of renal insufficiency (uremides or nephritides). It can be said that eruptions resembling erythema multiforme are extremely rare, and the literature contains but few authentic instances illustrating this combination; nor is it always clear that both occurred in close temporal relation. There are cases in which it appears that the onset of renal disease antedated by many months or years the appearance of erythema multiforme exsudativum or a rash resembling it, the cutaneous lesions having been seen in the period of azotemia; on the other hand, it is possible that erythema multiforme exsudativum may have an unfavorable influence on previously damaged kidneys for reasons to be mentioned later. It would seem that the entire subject is in want of fresh clinico-pathologic investigations.

On one point, however, there appears to be some certainty. Eruptions encountered in uremia are apt to become hemorrhagic. This phenomenon I have observed many times; for example, tinea cruris (eczema marginatum) may acquire a secondary hemorrhagic component during the course of an intense azotemia; scratch marks with superimposed linear hemorrhages may be a revealing sign of renal insufficiency; drug eruptions may assume a



sional cases showed rashes deviating from standard type, but conformity to textbook description cannot always be expected. To reject certain instances from this category because the thighs, for example, happen to be sites of predilection is to overlook natural variations in disease. Obermayer<sup>87</sup> and others have noted that in examples of erythema multiforme exsudativum affecting chiefly the mucous membranes, cutaneous lesions are apt to be encountered in atypical locations, as on the flexor surfaces (*typus inversus*). The crusting and "scaling" observed in some cases represented probably the sequelae of dried vesicles or collapsed bullae; the significance of these phenomena in erythema multiforme exsudativum has been previously discussed. Finally, recurrences have been met with in a number of cases,<sup>29, 70, 75, 83, 88</sup> and it is probable that the incidence of this feature would have been increased with greater opportunities for subsequent observation.

3. *Ocular Lesions Alone.* Hanke<sup>73</sup> recorded an instance of chronic membranous conjunctivitis (*herpes iris* of the eye), in which the lesions were restricted to that organ. In a condition with such protean manifestations this possibility may be conjectured. It is likely that study of the ocular alterations may reveal clinical criteria enabling the observer to diagnose the disease when limited to the eye, but this is a matter for future investigation.

C. *Other Mucous Membranes.* In addition to the parts already mentioned, other structures affected by erythema multiforme exsudativum are the nose, pharynx, larynx,<sup>89</sup> tracheobronchial tract, esophagus, glans penis, preputium, urinary meatus, urethra,\* labia minora, vaginal tract,<sup>90</sup> cervix, anus and, perhaps, the lower end of the rectum. Of interest is the report by Brünauer<sup>91</sup> who observed a number of such eruptions showing marked predilection for the male genitalia, especially the scrotum; in principle, however, the lesions were similar to those already described. It has been stated that the entire gastrointestinal tract may also be involved, but this localization cannot be accepted without considerable reserve, as there are ample opportunities for confusion with the Osler-Henoch-Schönlein group (*q.v.*).

Of special importance are the many instances in which the affection remained localized to the mucous membranes. For example, Crocker<sup>92</sup> reported a case of bullous erythema multiforme affecting the oral cavity, without involvement of the skin; subsequently, during one of the attacks, erythema iris lesions appeared on the backs of the hands, and then the patient recalled a previous similar occurrence. Butler<sup>93</sup> described an example showing four recurrences of the vesiculobullous variety of the disease, with involvement of the skin and oral cavity; the fifth attack, which was febrile in type, was limited to the buccal, lingual and labial mucous membranes, the

\* In a recent case under my observation a young physician had had several attacks of erythema multiforme exsudativum, sometimes with involvement of the mucous membranes. While in Switzerland, Dr. Bruno Bloch confirmed this diagnosis. The interesting feature was the occurrence of an intercurrent urethritis, the cause of which was not clarified. The relation of this phenomenon to erythema multiforme exsudativum was apparently never suspected, and it seems probable that some of the cases of non-specific urethritis may belong in this group.

as isolated lesions may be present even though there are no subjective symptoms attributable to them. On the other hand, oral manifestations may be the only or the most striking feature in this disease, especially in the vesicobullous form. It is not rare to encounter instances in which these parts are affected early in the course, with cutaneous lesions appearing later in that attack or in a subsequent recurrence.

Casual study of the efflorescences in the mucous membranes would seem to reveal attributes differing from those observed in the skin; yet these differences are not fundamental, but rather related to the modifying influence induced by anatomical relations. In addition, the factor of inaccessibility to direct and prolonged examinations often handicaps the observer. In the mucous membranes, notably of the mouth, variations in color and shade are less evident; scales and crusts are not as readily formed; atrophy and scarring are recognized with less facility. More important, vesicles and bullae are rarely found intact, for the structure of the mucous membrane is looser than is the case in the skin, permitting more active penetration by exudative products, and the layer corresponding to the horny portion of the epidermis lacks the cohesion required to allow an accumulation of fluid beneath it in restricted compartments. Moreover, such local modifying factors as moisture and warmth, the maceration of sputum, and the trauma of chewing, and movements of the tongue aid in distorting the clinical appearances. Many types of lesions, therefore, acquire the form of superficial erosions. In the eyes, also, the influence of moisture and blinking probably plays a part in changing the attributes of the efflorescences. Finally, secondary infection often occurs as a complicating factor capable of inducing profound alterations in the original aspects of these manifestations. Aside from a few typical appearances, it may be laid down as a good general rule that the diagnosis of oral lesions often rests on exclusion and on the observation of an eruption in the skin. Nevertheless, closer study may reveal better criteria for the recognition of a large proportion of the manifestations found in the mucous membranes.

*A. Oral Mucous Membranes.* The early dermatologic literature contains sporadic references to the oral lesions seen in erythema multiforme exsudativum (Bazin, Lipp, Charlouis, etc.). It was Quinquaud,<sup>10</sup> however, who furnished the first comprehensive description of these changes, and subsequent observations have been concerned merely with additional morphologic details. Quinquaud recognized an initial erythematous stage, the enanthem appearing as small red spots, round or oval in shape, and persisting in this form only a few hours. This is followed by the formation of vesicles and bullae. Owing to the local factors already enumerated, the efflorescences become superficially eroded, covered by a whitish membrane or fringed by fragments of torn epithelium, and circumscribed by an erythematous border. Finally, healing takes place, without the production of sequelae, though brownish macules marking former sites of enanthem may persist several weeks. Occasionally faint white scars may be observed,<sup>54</sup>

casionally a lymphadenopathy of moderate degree. Thus, it becomes evident that in the early stages, before the appearance of characteristic lesions in the skin and mucous membranes, the clinical picture may closely resemble a host of other affections. In addition, the common prodromal complaints may also occur at the height of the disease or during any part of its course. For this reason it seems advisable to analyze the constitutional manifestations according to the system involved.

*a. Upper Respiratory System.* Antecedent angina is a common prodromal complaint, being usually attributed to the presence of lesions in the posterior part of the oral cavity or in the pharynx. In some instances, however, sore throat may precede the appearance of the exanthem or even the enanthem by as long a period as one or two weeks; at this time the condition may occur in the form of a simple red throat and, indeed, there may be hardly any objective evidence of local pathologic alterations. Although it is not rare to encounter cases showing a few asymptomatic lesions in the oral cavity, the presence of such efflorescences generally produces subjective symptoms moderate in intensity, occasionally pronounced. When the enanthem is widely distributed the outstanding features may be pain on ingestion of food, salivation, or dysphagia; the odor of the breath may be extremely fetid, as in pemphigus.

Involvement of the tracheobronchial tract and its finer radicles is generally accompanied by mild or severe bouts of coughing. It is in such instances that every nursing precaution must be utilized to overcome the possibility of a superimposed bronchopneumonia, especially in elderly people.

In rare cases the disease has been known to involve the esophagus, causing a sensation of burning localized roughly in that part. There are also recorded occasional examples featured by implication of the larynx; such patients generally show symptoms of transient acute laryngitis,<sup>89, 94</sup> but the complaints may vary from none in those revealing isolated lesions on laryngoscopic examination to marked interference in breathing in those having tumor-like plaques or ulcerated areas. It is probable that more thorough search at postmortem examination would yield a higher incidence of such lesions.

The nasal passages, especially the external nares, are often involved in this disease. There is usually local discomfort, mechanical difficulty in breathing, and a discharge that is serous, mucopurulent, tinged with blood, or frankly hemorrhagic due to traumatic detachment of superficial crusts.

Hemorrhagic or blood-tinged sputum is often encountered incidentally; it may result from pathologic changes in any part of the respiratory tract for reasons already outlined.

*b. Fever.* In the vesiculobullous variety of erythema multiforme exsudativum it is common to observe some increase in the temperature, occasionally a remittent type of curve, and in some cases the clinical picture of a severe febrile disease. The temperature may attain a height of 104° F. or even 105° F., and to this variant, characterized by pronounced constitu-

sudativum. It is important to stress that healing may occur in one area while the disease progresses in another; thus, the oral lesions may fade completely, while extension along the tracheobronchial tract takes place.

The foregoing description indicates how frequently the enanthem may present appearances simulating other dermatoses; in such instances the diagnosis must be deferred until such time as a more precise idea of the clinical course is obtained or other "revealing signs" appear.

*B. Lesions in the Eye.* Involvement of the conjunctiva, rarely the cornea, occurs more often than is generally supposed. Such instances were described in the older dermatologic literature,<sup>60, 8, 37</sup> but these represented mild cases in which the conjunctivitis was more or less regarded as an epiphenomenon. To v. Düring,<sup>40</sup> in particular, credit is owing for the first comprehensive account of this manifestation, observed by him in about three-fourths of 122 patients showing erythema multiforme exsudativum. The conjunctival lesions generally appeared several days after the onset of the exanthem, though occasionally they antedated it. There were more or less circumscribed symmetrical areas, about a millet-seed in size, situated in the bulbar conjunctiva on the line of opening of the lids, especially on the temporal sides. These spots were roughly triangular in shape, elevated, colored yellowish or light gray with a superimposed reddish tint, attributed to the presence of injected conjunctival and, perhaps also, subconjunctival vessels. The lesions were practically always bilateral. The remainder of the conjunctiva usually showed some degree of hyperemia. In other cases a catarrhal condition was superimposed, the patients complaining of burning, itching, tearing, mild photophobia and, occasionally, of a mucoid or mucopurulent discharge. The course was acute, healing occurring in from two to three weeks, without the production of residual changes. There were occasional local relapses that ran a similar course. Once keratitis was encountered, but this resolved completely. The outcome was, therefore, favorable in this group of patients. It was also observed that, when the cutaneous lesions affected the region of the eyes, the lids were swollen, notably the upper lids—an occurrence noted by many later writers.<sup>67, 68, 45</sup> Other investigators described a mild type of conjunctivitis in which, by the aid of a magnifying lense, small vesicles could be recognized,<sup>69, 70</sup> while still others mentioned coryza as one of the early symptoms of erythema multiforme exsudativum<sup>37</sup> or referred to banal forms of vascularization (hyperemia) of these parts.<sup>71</sup> Chevalier and Toulant<sup>72</sup> encountered an example showing a positive fluorescein test, despite which there was total restitution to normal, illustrating the essential benignity of the changes in this case; in addition, they found other alterations which they regarded as evidence of episcleritis. Instances showing conjunctival bullae were also occasionally observed, and the similarities to pemphigus of the eye were discussed. So far as the dermatologic literature was concerned, these were the most important changes described, and they were encountered in patients showing the papular or papulovesicular forms of erythema multiforme exsudativum, with or with-

yet, to warrant drawing of definite conclusions, but this method of investigation should be employed more extensively.

*e. Gastrointestinal System.* My observations indicate that colic is neither a frequent nor a significant feature in erythema multiforme exsudativum; when this has been claimed, it seems evident that the affection has been confounded chiefly with the Osler-Henoch-Schönlein group, etc., etc. In one instance under my observation abdominal pain occurred, but this seemed to be caused by the coincidental presence of a painful ovarian cyst. Occasionally blood may be found in examinations of specimens of stool; this is generally caused by the swallowing of débris of superficially eroded lesions in the oropharynx, and nose; rarely, it results from lesions in the lower portion of the gastrointestinal tract. Under such circumstances the finding of a positive guaiac reaction in the stools is less significant, and this epiphenomenon cannot be regarded as the pathological equivalent of the process observed in the Osler-Henoch-Schönlein group of affections.

*f. Urinary Tract.* Involvement of the kidneys (inflammatory, degenerative or vascular) appears not to be an essential part of erythema multiforme exsudativum. I must therefore agree with Tachau<sup>27</sup> that the belief in the simultaneous occurrence of renal disease arose from the inclusion of many cases that do not properly belong in this category, for example, "systemic" lupus erythematosus.<sup>4</sup> When albuminuria is discovered it represents generally part of a febrile response or a coincidental finding. Hematuria, observed in occasional instances, is often caused by erosive inflammation of the urethral and preputial surfaces; this evidence per se cannot be regarded, therefore, as indicating involvement of renal tissue. By the same token, the occurrence of hypertension is probably coincidental and unrelated. The influence of renal failure on the morphology of other cutaneous lesions has been discussed in a previous section.

*g. Lymphadenopathy.* Generalized enlargement of the superficial lymph nodes is sometimes encountered,<sup>12, 45, 138, 153</sup> but it rarely attains an extreme grade.<sup>12</sup> When present, the glands are usually moderately enlarged. Düring<sup>40</sup> observed enlargement of the cervical nodes in an appreciable percentage of his cases; this is to be expected in instances showing secondary infection in the oral lesions. It is to be stressed, however, that lymphadenopathy may be encountered in the absence of such complicating factors. In one instance under my care the right pre-auricular node reached the size of a large bean, the remainder of the superficial lymph glands being smaller, though palpably enlarged. I have also observed several examples in which the lymphadenopathy was sufficiently pronounced to suggest the possibility of infectious mononucleosis. It is probable that occasional instances may show involvement of the hilar glands<sup>153, 102</sup>; for example, Liebner<sup>102</sup> found hilar shadows in four out of 15 cases of erythema multiforme exsudativum. The precise significance of these findings is, however, still uncertain.

*h. Splenomegaly.* Moderate enlargement of the spleen is sometimes encountered.<sup>21, 40, 45</sup> This I observed once, the organ being felt, as a mod-

panied usually by a marked discharge of purulent or non-purulent nature; when the condition is more pronounced the intervening parts of the conjunctivae and bulbar portions are also affected. This division into variants is arbitrary, as there are transitional clinical pictures. Instances showing membranous or pseudomembranous conjunctivitis with few or no residual changes have been recorded by Fuchs,<sup>42</sup> Hanke (second case),<sup>73</sup> and Hartlev<sup>77</sup> among others; these were associated with typical oral and cutaneous lesions, and it is noteworthy that the course was afebrile in the examples reported by the first two observers cited. Next in severity were the instances described by Raffin<sup>78</sup> and by Stark<sup>79</sup>; in the first one, several white scars were found in the palpebral conjunctivae of the upper lids, while in the latter there were noted, some four years after onset, grayish deposits on the tarsal conjunctivae, nebulae, and clouding of the corneae. Barkan's patient<sup>80</sup> had residual chronic alterations causing ankyloblepharon, symblepharon, and corneal opacities producing blindness. Finally, at the opposite end in the scale are the cases reported by Stevens and Johnson,<sup>29</sup> Wheeler,<sup>81</sup> Rutherford,<sup>82</sup> Bailey<sup>83</sup> and Ginandes<sup>84</sup> among others; in these instances blindness was an outstanding complication during the acute phase of the affection. In some of the patients it was considered essential to remove an eye owing to fear of panophthalmitis. Practically all revealed evidence of oral and cutaneous lesions, and in some there was additional involvement of other mucous membranes. Deaths were recorded in the patients seen by Smith<sup>85</sup> and by Hanke,<sup>73</sup> the immediate cause being severe bronchopneumonia.

#### THE STATUS OF THE STEVENS-JOHNSON SYNDROME

The group of cases showing severe ocular manifestations have been classified popularly under the category of Stevens-Johnson disease,<sup>29, 84</sup> the original belief being that this was a hitherto undescribed affection. Preliminary data have been furnished to indicate that these examples represent only a variant of erythema multiforme exsudativum, and the intention now is to complete the account with an analysis of a few features of special interest.

1. *Age of Patients.* Most of the cases showing severe or relatively severe ocular manifestations concerned children; young adults and occasionally older persons were also affected. Whereas, therefore, no age seems to be spared, it appears that children are apparently predisposed to the graver forms of the condition.

2. *Cutaneous Lesions.* Although occasional instances showed pure papular eruptions<sup>81, 82, 83</sup> or combinations of papular and vesiculobullous efflorescences,<sup>73</sup> the vast majority were accompanied by markedly exudative cutaneous lesions. Typical herpes iris of the skin was encountered in some cases,<sup>42, 73, 75, 78</sup> bullae with serous fluid in others,<sup>77, 79</sup> and hemorrhagic bullae in still others.<sup>80, 84, 86</sup> In several instances the dermatosis was generalized in extent and, in particular, covered the entire trunk.<sup>73, 74, 81, 82, 83, 84</sup> Occa-

least one case,<sup>68</sup> a man of 20, the patient recovered completely from the attack. The essentially benign course of the affection is shown especially in those instances manifesting seasonal recurrences.

#### ESSENTIAL DIFFERENCES BETWEEN TACHAU'S ACCOUNT AND THE DATA IN THIS PAPER

In summarizing the controversial aspects of this subject, it seems pertinent to indicate briefly the outstanding points of debate; in this manner fundamental distinctions are likely to stand out in bold relief, and such differences may serve as the basis of further investigation. The most representative of the numerous European publications concerned with this subject is that of Tachau<sup>27</sup> who adheres to the views held by the old Vienna school. To summarize the essential points of dissimilarity:

1. Tachau does not admit the occurrence of fatalities and even denies the authenticity of cases illustrating a severe clinical course. The data recorded in this paper appear not to substantiate this fundamental contention.

2. Tachau, although admitting the occurrence of microscopic extravasations of red blood cells, denied the possibility of gross visible hemorrhage into the lesions. It is my belief that such an absolute statement is not justified.

3. Tachau's account of the lesions in the eyes is confined to the mild manifestations, the implication being that the severe cases belong to another category of disease. The data recorded in this paper are at variance with the above belief. In arriving at this conclusion I have followed Tachau's rule that atypical manifestations are to be regarded as part of the affection only if observed with some regularity in association with typical features of erythema multiforme exsudativum.

4. It is, therefore, understandable that Tachau differentiates the clinical pictures described by Fiessinger and by Baader from that seen in erythema multiforme exsudativum. This point of view seems unacceptable for the reasons already mentioned in the paragraphs devoted to a consideration of these syndromes.

#### DIFFERENTIAL DIAGNOSIS

The outstanding diagnostic features are revealed by the lesions in the skin and mucous membranes. The systemic manifestations are, on the other hand, banal; yet, it is essential to recognize them, if only for their negative attributes. At this point two legitimate questions may be asked. (1) Can erythema multiforme exsudativum be diagnosed solely on the basis of a single or a few cutaneous lesions? In such instances it appears that this disease may be strongly suspected provided the morphology of the individual efflorescences corresponds to the descriptions already furnished, but it is wise to suspend judgment until such time as the clinical course can be better evaluated. (2) Are the mucosal lesions recognizable per se? While

integument having been spared. Such instances could be multiplied many times.

### THE STATUS OF ECTODERMOSIS EROSIVA PLURIORIFICIALIS

The foregoing data support the belief that the cases reported under this title <sup>28, 29, 30, 31, 32, 76, 95, 96, 97</sup> merely represent variants of erythema multiforme exsudativum, characterized by preponderant involvement of the various mucous membranes, including the conjunctivae. Jausion and Diot,<sup>98</sup> reporting two examples of this syndrome, concluded that their cases, as well as those described by Fiessinger and his co-workers, belonged in the category of Bazin's<sup>8</sup> *hydroa vésiculeux*; the latter, according to the data in this paper, is one of the names used in France for vesiculobullous erythema multiforme exsudativum. In many cases there were cutaneous manifestations showing typical morphology; in a large proportion of instances recurrences were noted subsequently <sup>28, 34, 70, 95, 96</sup>; in others there were relapses <sup>97</sup>; and at least one observer stressed the seasonal incidence of the attacks.<sup>95</sup> My views are, therefore, in close agreement with the opinions expressed by Klauder<sup>28</sup> and by Kumer<sup>96</sup> who believe in the essential grouping of this syndrome under Hebra's erythema multiforme. The controversy between Baader,<sup>34</sup> who regarded his cases as representing a new entity, and Moncorps,<sup>33</sup> who classified the clinical picture as a "grippe" exanthem, is illustrative of the confusion that has crept into the literature when undue significance is attached to slight deviations from the normal or average textbook descriptions.

### SYSTEMIC MANIFESTATIONS

Thus far stress has been laid on those lesions on the basis of which the disease is chiefly recognized. In many instances the clinical picture is actually dominated by systemic features of more or less banal type, their occurrence tending to confuse rather than to clarify the diagnosis. During any individual attack of either papular or vesiculobullous erythema multiforme exsudativum constitutional symptoms may be absent; this is much less often the case in the latter type. There are, however, imperceptible transitions between the severe instances and those manifesting systemic features of minimal intensity; and, contrariwise, the papular variety may occasionally be accompanied by a pronounced constitutional reaction.

*Prodromal Symptoms.* A detailed study of erythema multiforme exsudativum reveals the protean nature of its manifestations, notably those occurring at the inception of the disease. Though it is common to describe prodromal symptoms, the order of appearance is irregular and unpredictable, depending on the severity, the extent and the particular system first affected. The early manifestations create the clinical impression of an "upper respiratory infection" in most instances, such patients complaining of one or more of the following symptoms: sore throat, bronchitis, laryngitis, irregular fever, nasal discharge, coryza, joint pains, slight headache, malaise, and oc-



in a precise category, and substantiation of this observation awaits further study in fresh cases. The common finding of enlarged hilar nodes ("hilitis") in erythema nodosum is probably also duplicated in erythema multiforme exsudativum,<sup>102</sup> though to a much lesser degree; it is, therefore, difficult to be certain of whether this can be used as a differentiating feature, the more so as roentgenograms of the chest are more often taken in the former affection in view of the prominent part played by the tuberculous theory of erythema nodosum, whereas such studies are but rarely pursued in erythema multiforme exsudativum. Nor am I certain that a marked tuberculin reaction, even in graded dosage, is sufficiently characteristic to distinguish these diseases. These points, among others, require further investigation for precise evaluation.

The differential diagnosis between these affections becomes confusing under the following uncommon circumstances. (1) There are cases of genuine erythema nodosum accompanied by lesions on the face and other parts, where exudative attributes (especially vesiculation) are occasionally observed; of this variant I have encountered two striking examples, and others, such as Adamson, have recorded additional examples. (2) Erythema multiforme exsudativum may be accompanied by lesions on the lower limbs, where, owing to the influence of anatomical peculiarities, these efflorescences are apt to be somewhat nodular, to show a cyanosed hue and to reveal tenderness on palpation. This point has already been elaborated in a previous section in which it was also noted that these attributes are manifested by a large number of dermatoses. It is this type that is often described as erythema multiforme exsudativum combined with erythema nodosum. Despite these occurrences it would be unwise at present to regard the febrile forms of these affections as identical without further study of so-called transitional examples. In the section devoted to the resembling forms of tuberculides of the skin there will be described an eruption that has been confused occasionally with these "transitional" cases. In its classical form, erythema multiforme exsudativum is a well-characterized disease that differs radically from idiopathic erythema nodosum in the location, morphology and clinical course of its cutaneous and mucosal manifestations.<sup>39</sup>

3. *Osler-Henoch-Schönlein Syndrome* ("Capillary Toxicosis" of Frank). It will be remembered, as a point of historical interest, that Osler in one of his earlier papers on this subject used the term erythema multiforme exsudativum to describe the cutaneous manifestations. While the eruptions encountered by him were truly polymorphous, it is a tribute to his clinical ability that he later dropped this term and substituted for it the more non-committal name of "erythema group." In several other publications<sup>1, 4, 104</sup> I have discussed the conception of this affection and have presented data indicating that the clinical pictures described by Schönlein, by Henoch, and by Osler appear to fall into a single category corresponding essentially to "capillary toxicosis" in the sense of Frank. The average example of this affection presents distinctive cutaneous and internal medical

tional symptoms, Lortat-Jacob<sup>25</sup> gave the name "intense pyretic form" of erythema multiforme exsudativum. It must be stressed that occasionally the papular form of this affection may be attended by a severe febrile illness, though this is relatively uncommon. The irregularities in the temperature are so marked that it is difficult to speak of a typical fever curve, and this inconstancy is often betrayed in the variations exhibited in the relapses and recurrences. In many cases, especially in the erythemato-papular type, the temperature is normal, but too much reliance must not be placed on the subjective well-being of the patient, for in a few such instances I have been able to detect slight degrees of fever (up to 100° F.). It has been stated<sup>36</sup> that children afflicted with this affection are prone to manifest signs of an intense constitutional reaction; this rule, however, admits of many exceptions.

*c. Articular Involvement.* In many cases this manifestation is absent, but it is essential to question the patient carefully in an effort to discover the mild examples of this affection. When joint pains are encountered they are usually of the nature of arthralgias, designated more generally as "rheumatoid" or as "pseudo-rheumatic" for the purpose of differentiating them from true rheumatic articular disease. Evidence of periarticular involvement is uncommon, except apparently in cases where the small articulations are affected,<sup>51</sup> and still more rarely does an intra-articular effusion appear. I have not encountered any instance in which the fugitive, migratory polyarthritis characteristic of rheumatic fever in the corresponding age-group was truly simulated.

*d. Involvement of the Heart.* Cardiac murmurs are sometimes heard at the apex or the base of the heart, but in no instance under my observation did valvular defects result therefrom. The older statistics<sup>15</sup> on the incidence of endocarditis in this affection are unreliable, as they were compiled at a time when little effort was made to differentiate the host of diseases included under the generic title of erythema multiforme. Moreover, the diagnosis of organic valvular disease was based chiefly on the presence of a murmur at the apex or base of the heart, in many instances probably accidental or functional in nature. The essential point was recognized by Teissier and Schaeffer<sup>99</sup> who concluded that in many cases of "erythème polymorphe," these murmurs were "extra-cardiac" in origin; that the incidence of endopericarditis was very small; and that, contrary to the opinions expressed by Garrod<sup>100</sup> and by Lewin,<sup>15</sup> genuine valvular defects belonged to the rarities. It will be seen, from consideration of the data recorded in my various publications, that the discordance in views can be attributed to the different types of dermatoses studied, for Teissier and Schaeffer were probably concerned with erythema multiforme exsudativum; Garrod, in the main, with rheumatic erythema multiforme; and Lewin, with a heterogeneous group of conditions. No instance of erythema multiforme exsudativum has come under my observation, thus far, where electrocardiographic studies revealed significant alterations, this being equally true of the cases recorded by Meyer<sup>101</sup> under a different title. Fluoroscopic data are too meager, as

probably not an essential part of the disease, but rather represent a sequel to lowering of the patient's local or general resistance; the former event occurred in one striking case under my observation where secondary infection of hemorrhagic oral lesions played a notable part in causing a fatal issue. Considered in terms of the composite clinical picture, the differentiation is difficult only in occasional instances.

4. *Systemic Lupus Erythematosus*. The well-developed case of systemic lupus erythematosus shows a multiplicity of distinctive cutaneous and internal medical features that may be regarded as practically pathognomonic of this disease. A more complete account of these manifestations will be found in several other publications,<sup>1, 4, 106, 107, 108</sup> and to these data I have added, in the appropriate sections in this article, additional points relative to simulating eruptions encountered in a large number of instances of erythema multiforme exsudativum, particularly in its vesiculo-bullous form. As the subject will receive more detailed consideration in a forthcoming monograph, this section will be concluded with mention of two interesting points. (1) There are cases which are diagnosed in the early stages as erythema multiforme, owing to the occurrence of lesions situated chiefly on the extensor aspects of the limbs, which subsequently develop the full-fledged picture of systemic lupus erythematosus. In some cases this differentiation is indeed difficult, but a relatively short period of observation generally suffices to resolve this problem. (2) The factor of coincidence must always be taken into consideration; for example, drug rashes simulating erythema multiforme exsudativum may in rare instances complicate a preëxistent lupus erythematosus. It is essential, therefore, that every case be evaluated meticulously and that coincidental factors be relegated to their proper place.

5. *Bacteremia*. In a recent publication Bingold<sup>109</sup> discussed the problem of erythema multiforme exsudativum in connection with dermatoses encountered in the course of various types of bacteremia. Whereas "septic" eruptions may be considered broadly as polymorphous in their clinical attributes, the resemblances between them and erythema multiforme exsudativum are, in my opinion, based on superficial analogies. For example, gonococcal bacteremia is occasionally accompanied by a peculiar type of rash displaying multiformity in the cutaneous lesions, and hence called "erythema multiforme"; my observations<sup>2</sup> indicate that these efflorescences, which are caused by the gonococcus, may be differentiated with comparative facility in most instances from erythema multiforme exsudativum, and in advance of a positive culture of blood. This is particularly true if the clinical attributes of the rash are correlated with the internal medical manifestations. This observation leads inevitably to the principle, recognized by Bingold and others in a preliminary way, that the various types of bacteremia are often accompanied by highly characteristic eruptions, and that recognition of these cutaneous lesions may enable the observer to diagnose not only the presence of bacterial invasion of the blood stream, but also, in many cases, the nature of the causative organism. It is my intention, in the future,

erately firm structure, about one finger's breadth below the costal margin; with resolution of the disease the spleen receded.

*i. Blood Findings.* In the average afebrile case there are no definite abnormalities in the blood-count. In the intense pyretic form and in the presence of such complications as bronchopneumonia there are variable degrees of leukocytosis, with an increase in the polymorphonuclear leukocytes. Eosinophilia is an uncommon coincidental finding. In a few instances, as in two cases under my observation, there was a moderate degree of leukopenia with relative lymphocytosis; the occurrence of palpably enlarged lymph nodes suggested the possibility of infectious mononucleosis, but the heterophile reaction was negative. Mild secondary anemia occurs occasionally, and there are no significant alterations in the blood platelets. In a few instances I have observed a local eosinophilia in bullous lesions, but the banality of this phenomenon depreciates its significance for diagnosis. There are many cases showing marked variability in the blood-counts made during the initial attacks and in the recurrences. In summary, the findings in the blood seem to shed but little light on the nature of the affection.

#### PROGNOSIS

Hebra<sup>9</sup> emphasized the benign nature of the disease, though he had seen one case terminate in pneumonia. There are observers, among whom Tachau may be mentioned, who deny the occurrence of severe complications as an essential part of the affection and therefore reject the so-called malignant form of erythema multiforme exsudativum. It is undoubtedly true that numerous lethal cases have been classified erroneously in this category when, in reality, they represented examples of acute "systemic" lupus erythematosus, "capillary toxicosis" of Frank, and other conditions. Nevertheless, I have seen fatalities occur in a number of authentic cases of erythema multiforme exsudativum, owing to: (1) bronchopneumonia secondary to aspiration of decomposed and infected material in the oropharynx, notably in elderly people; (2) simultaneous involvement of the tracheobronchial tract with superimposed bronchopneumonia; (3) an intercurrent complication which may be related only in the sense that there is lowering of the patient's local or general resistance; (4) perforation of the eyeball, when the conjunctiva and cornea are intensely affected, leading to panophthalmitis and, perhaps (?), secondary invasion of the blood stream, especially in children. Blindness in one or both eyes, partial or total, represents the most common complication in these cases.

These data, therefore, indicate that the prognosis depends essentially on the degree of involvement of the various mucous membranes. In the vast majority of cases recovery is the rule, despite the clinical impression of severe toxemia in some instances. This point was well illustrated in the five examples of this disease reported by Eisenstaedt,<sup>53</sup> recovery ensuing though the patients seemed to be desperately ill. In rare instances of the severe form of the disease there may be encountered psychotic manifestations<sup>68, 135</sup>; in at

in erythema multiforme exsudativum. Ocular involvement of the nature of essential shrinkage of the conjunctivae may appear in both affections and, probably also, in other diseases, though the condition is most commonly encountered in pemphigus. Early in the course a few aberrant bullae in erythema multiforme exsudativum may be lacking in the usual erythematous halo, and, contrariwise, it is not unusual to observe an inflammatory reaction about isolated lesions in pemphigus of the skin in advanced stages. The age incidence, the Nikolski sign (detachment and fragility of the superficial epidermis following the trauma of rubbing the skin), and the phytotoxic test (Pels-Macht) are probably not decisive in judging individual instances or in establishing an absolute diagnosis. There may be an exception to the preceding statement in that pemphigus is much less likely to affect young adults, though there are probably exceptional examples. Histologic examination often provides differential diagnostic data, but whether this is also true in atypical cases cannot be stated with confidence at present. The common complications and causes of death in erythema multiforme exsudativum have been mentioned in the section on prognosis; in pemphigus fatalities result generally from bronchopneumonia, "toxemia," exhaustion or "cachexia," terminal bacteremia and other complicating infections such as tuberculosis,<sup>111</sup> and, rarely, perforation of gastrointestinal ulcerations. There are, however, many examples where even a complete postmortem examination fails to shed light on the cause of death or to furnish the slightest information on the nature of the essential process.

It follows, then, that there are occasional instances in which these diseases cannot be distinguished on the basis of the observation of a few lesions, and a probable opinion can be formulated only on a consideration of the attributes shown by the composite eruption and the general clinical course. In most cases, however, these processes are fairly distinctive; it is essential always to eliminate the possibility of drug eruption. I have seen a number of patients presenting oral lesions, concerning which opinions fluctuated between the diagnosis of erythema multiforme exsudativum and pemphigus; the vexing problem was finally resolved by the subsequent appearance of the cutaneous efflorescences characteristic of the respective diseases. Chronicity in the evolution of individual lesions is a feature encountered consistently in pemphigus, and this property is especially seen in the case of efflorescences situated in the integument. A history of preceding weakness, poor health, marked loss of weight, etc., prior to the appearance of the exanthem or enanthem point in the direction of pemphigus, but each case must be individualized.

According to Kinnear<sup>112</sup> and Levin, Tolmach and Schweig,<sup>113</sup> there is a variety of pemphigus vulgaris exhibiting the features of "erythema multiforme." I submit, on the basis of the data previously described, that no convincing proof has been offered in substantiation of this thesis; that this view is based on a paucity of atypical examples diagnosed on the basis of doubtful criteria; that, included in this group, are some typical instances of

there are observers who may be inclined to doubt this and while it is true that these manifestations may be simulated closely by a host of other affections, it is my belief that erythema multiforme exsudativum confined to the mucous membranes, especially of the mouth, may be recognized in a high percentage of cases on the basis of the appearances exhibited in these parts and the concomitant general clinical picture. When the disease has an acute onset and short duration there may be genuine diagnostic difficulties that are generally overcome, however, by further observation.

It is my intention in the ensuing section to restrict the discussion of the differential diagnosis to the affections that I have encountered in private practice, dispensaries and medical wards.

1. *Rheumatic Fever*. Throughout the history of erythema multiforme exsudativum the question of "rheumatism" has loomed large owing to obscurities in conception and nomenclature. At the outset it may be noted that the cutaneous lesions in rheumatic fever rarely, if ever, show a vesicular, pustular or bullous component; in the excessively rare instances where such phenomena were described, the diagnosis of rheumatic fever was doubtful or the rash could be attributed more properly to another cause.<sup>3</sup> On the other hand, erythema marginatum rheumaticum presents certain resemblances to the marginated form of erythema multiforme exsudativum. The former differs, however, in its more rapid onset; striking predilection for the trunk; remarkable changes in configurations within short intervals of time, generally measured in hours, occasionally in days; occurrence in successive crops over days, weeks or even longer; appearance chiefly in children; and in the association with rheumatic stigmas, such as organic cardiac disease, subcutaneous nodules and chorea. This subject is discussed in greater detail in another place.<sup>3</sup>

2. *Erythema Nodosum*. The average example of erythema nodosum shows distinctive cutaneous lesions and clinical course. The mucous membranes are spared, though in a number of instances I have seen the eyes affected in the form of wedge-shaped episcleritis as well as milder examples of what is commonly described under the broad title of "phlyctenular conjunctivitis"; these lesions were essentially benign and disappeared without leaving sequelae. A few observers have apparently noted involvement of the oral mucous membranes in the form of erythematous nodules, but such manifestations belong to the curiosities of medicine. I have not encountered any instance of severe conjunctival or corneal lesions simulating those found in erythema multiforme exsudativum. Occasional writers have observed hemorrhagic efflorescences under the nail plate (Verco's sign) in erythema nodosum. It is of interest that similar lesions were found by Schere-metjew<sup>103</sup> in a case of "polymorphous exudative erythema," featured by an eruption on the face, backs of the hands, external aspects of the legs; fever; recurrent crops of what was interpreted as erythema nodosum of the legs; glands in the neck, submaxillary, axillary and inguinal regions; joint pains, etc., etc. It is, however, exceedingly difficult to classify this instance

the formation of atrophic or scarred areas in the skin and oral cavity; the formation of milia or pseudo-milia is a common sequela that is, however, not pathognomonic; (5) the origin of lesions at sites of pressure and their frequent reproduction by mechanical traumas; (6) the appearance of hemorrhagic bullae. In typical examples the clinical picture is distinctive. In the past too much reliance has been placed on the finding of diminished or absent elastica fibrils in microscopic sections of affected and unaffected skin, but the technical difficulties in staining, the discordance in the histologic interpretations, and the lack of adequate controls are a few factors that warrant circumspection in evaluating this type of evidence.

As stated, the cases showing involvement of the eyes are the ones presenting the closest similarities to erythema multiforme exsudativum. A review of the literature bearing on this phase of the subject reveals that, whenever complete clinical details were furnished, the case was of the dystrophic type,<sup>117, 118, 119, 120, 121, 122</sup> rather than the simple form of epidermolysis bullosa (nails affected in nearly all cases, familial occurrence of the disease, inception at an early age, etc., etc.). The few exceptions to this rule are the examples recorded by Bogrow<sup>124</sup> and by Cohen and Sulzberger<sup>123</sup> and it is precisely in these instances that the diagnosis of epidermolysis bullosa, though probable, was not absolute. Thus, in the case described by Sulzberger and Cohen, an instance which I had the opportunity of observing several times without being able to classify it precisely in my own mind, the aforementioned features of typical dystrophic epidermolysis bullosa were generally lacking. This was also true in the example recorded by Bogrow<sup>124</sup> and, indeed, this observer apparently had doubts in his own mind as to the classification of this instance. In both cases there were cutaneous lesions that simulated strongly those seen in erythema multiforme exsudativum. It suffices to state, then, that in contradistinction to Duke-Elder's account,<sup>125</sup> these atypical examples must not be regarded as proved beyond cavil. Essential shrinkage of the conjunctivae seems to be a syndrome caused by several affections, of which the most common are pemphigus, epidermolysis bullosa, erythema multiforme exsudativum and, perhaps, other diseases. It must be admitted, however, that "cicatricial atrophy" and the resultant secondary trichiasis are probably encountered more often in dystrophic epidermolysis bullosa than in erythema multiforme exsudativum, though these pathologic alterations are not absolutely distinctive. It is evident that a renewed interest in the ocular lesions observed in these diseases is essential before more precise interpretations can be offered.

*10. Drug Eruptions.* In another publication<sup>30</sup> I have discussed some of the difficulties encountered in differentiating drug eruptions from erythema nodosum; here it is my intention to mention a few principles that hold analogously in the case of erythema multiforme exsudativum.

A variety of drugs may produce eruptions that fall within the bounds of the broad definition of erythema multiforme as given in the first part of this paper. With occasional exceptions such rashes do not resemble closely

features. In comparison with these lesions involvement of the mucous membranes, including the eyes, is comparatively uncommon, though important for reasons that will be mentioned in another publication. It is not my intention, at present, to describe the various polymorphous rashes associated with capillary toxicosis, but rather to restrict the discussion to the so-called "erythema multiforme-like" type of lesions (erythematous papules) commonly observed in the affection, as this is the variety most likely to be confused with erythema multiforme exsudativum.

In capillary toxicosis the cutaneous lesions show a striking propensity to affect the areas about the joints (in the order of frequency: ankles, knees, elbows, wrists, hips, shoulders, etc.), although outlying parts may also be involved, and, least commonly, the trunk and face. As there are occasional instances of erythema multiforme exsudativum exhibiting eruptions confined, for the most part, to similar areas, the differentiation would be difficult, were it not for the succeeding alterations that endow the lesions in capillary toxicosis with recognizable peculiarities. Thus, even early in the course there is a secondary hemorrhagic component which is often superimposed in the form of a central punctum, or as a minute hemorrhagic vesicle; or, what is more characteristic, subsequent crops of frank purpuric and petechial spots may entirely replace the "multiform" lesions, with similar favor for areas about the joints. Additional help is, moreover, afforded by the nature of the internal medical manifestations, the clinical picture being dominated often by two distinguishing features: (1) evidence of genuine renal disease, the nature of which will be discussed in another publication; (2) gastrointestinal symptoms pointing to involvement chiefly of the areas about the ileocecal valve. It must be stressed, however, that the finding of blood alone in the urine and in the stools is not necessarily clear-cut evidence of "capillary toxicosis," as this may be encountered occasionally in erythema multiforme exsudativum for reasons previously mentioned. I cannot, therefore, agree with Glanzmann in the classification of the third case described in his paper (1928)<sup>105</sup> as an example of erythema multiforme exsudativum, but, on the contrary, believe that the clinical features in that patient pointed clearly to the Osler-Henoch-Schönlein group (sore throat, fever, joint involvement, typical location of the crops of petechiae, intermittent attacks of colic, many bloody stools, etc.).

Finally, although spontaneous recovery appears to be the rule in "capillary toxicosis" and while the affection seems not to be nearly as grave as one would be led to infer from accounts in the literature, the prognosis, nevertheless, should be guarded in all instances. This holds especially for those cases characterized by evidence of severe renal or gastrointestinal involvement. A small, though definite, percentage of cases, estimated roughly at from 10 to 15, end fatally. The most important causes of death are: (1) renal insufficiency; (2) intussusception; (3) perforation of the small intestine leading to peritonitis; (4) intercurrent infections (especially in the rare instances affecting the mucous membranes) and unrelated infections that are



claim<sup>129</sup> that erythema multiforme exsudativum is of tuberculous nature requires careful consideration; this observer believed that he had demonstrated such an origin by using the method of multiple inoculations into guinea pigs. The reliability of this procedure and related investigations has been seriously questioned by some from the point of view of pure bacteriology; moreover, a few observers,<sup>130</sup> utilizing the technic advocated by Ramel, have been unable to substantiate the latter's results. At present there are reasonable grounds for concluding that decisive bacteriologic evidence indicating an alliance between these two affections is still lacking.

Clinically, however, occasional examples of "erythema multiforme" may be encountered in apparent relation to an active tuberculous process. Thus, there came under my observation an instance of tuberculous intracanalicular bronchopneumonia and meningitis in a child who showed symmetrical patches of erythema about the extensor aspects of the ankles and knees. This type of nondescript erythema is often classified as "toxic erythema" or as "erythema multiforme," both terms being employed in the broadest sense possible, and in this particular patient the precise relation between the cutaneous lesions and the tuberculous process remained obscure (toxic?, bacterial?). Of greater importance for the problem under consideration is the occurrence of a more acute variety of erythema induratum revealing transitions of papulonecrotic tuberculides and resembling either erythema nodosum, erythema multiforme exsudativum or combinations of these rashes.<sup>39, 131</sup> Of this variant I have had the opportunity to study three striking examples, characterized by the occurrence of cervical lymph node tuberculosis, typical papulonecrotic lesions, and painful, purplish red, nodular efflorescences on the lower limbs. The latter simulated ordinary erythema nodosum, the resemblances being further promoted by the failure to ulcerate and the assumption of an intense purple hue in the course of gradual involution. They differed, however, in their longer duration, in their association with typical lesions of papulonecrotic tuberculides (some of which failed to show the characteristic central necrosis), and in the presence of chronic active tuberculosis of the lymph gland variety. In some instances the necrotic centers may be so small and superficial as to create the effect of dried vesicles, and as the lesions may be situated on the dorsum of the hands and the extensor aspects of all the limbs, and as they may recur in many crops, the eruption often takes on features simulating Hebra's erythema multiforme exsudativum. Peculiarly enough, the three cases mentioned concerned women of middle age and beyond; all had subfebrile temperature during some part of the course, and all recovered, at least temporarily. Two of them were followed for many months; of these one had a draining sinus in the neck, which apparently healed after the use of ultraviolet and roentgen-ray irradiation, though this required a long time. However, almost one year later I ascertained that the cutaneous lesions had recurred on several occasions. Similar cases have been recorded by other writers under

to furnish evidence substantiating this principle. Before concluding this section, it may be mentioned that there are occasional instances of chronic meningococcemia featured by the appearance of erythematous-vesicular lesions on the upper limbs and elsewhere and that these may be confounded with the exudative variety of erythema multiforme exsudativum. This mistake I once made in a peculiar instance, and the lesson I learned was that in any patient exhibiting an atypical erythematous-vesicular eruption, associated with rises in temperature resulting in a prolonged intermittent or remittent febrile course, numerous attacks of polyarthralgias, and a remarkably good state of health despite the protracted course, the possibility of chronic meningococcemia should be given serious consideration. The importance of such a differentiation will be discussed in my publication dealing with the eruptions observed in the various types of bacteremia.

6. *Fuso-Spirochetal Disease*. The subject of Vincent's (fuso-spirochetal) disease is at present in a confused state, owing chiefly to the lack of genuine diagnostic criteria for its recognition. To classify a condition in this category on the basis of painful stomatitis associated with the finding, in a smear, of fusiform bacilli and spirochetes, even in large numbers, must inexorably lead to important errors in diagnosis. For example, I have encountered a number of cases in which these criteria were fulfilled, yet these concerned instances of leukemia in its acute phase, pemphigus, uremia, erythema multiforme exsudativum, etc. It is evident, from a critical perusal of the literature, that many unrecognized examples of erythema multiforme exsudativum are being labeled as Vincent's stomatitis with cutaneous lesions on the basis of doubtful criteria, as a result of which the remedy used in the particular case has come in for undue praise. Without analyzing the data in great detail, it seems likely that what at present may be termed primary fuso-spirochetal disease of the mouth (necrotic gingivitis and its variants) appears to be a fairly well-defined entity,<sup>110</sup> featured by (1) typical localization of the lesions; (2) fairly characteristic subjective symptoms and objective signs in the acute and chronic stages; (3) definite response to oxidizing agents in most cases, and, perhaps also, to the arsphenamines in severe instances. There is urgent need for close coöperation of dentists, internists, dermatologists, and bacteriologists for the purpose of more precisely determining adequate clinico-pathologic criteria for the recognition of Vincent's disease and its related affections. It is a subject that should be investigated from the ground up and nothing assumed as true unless substantiated beyond a reasonable doubt.

7. *Pemphigus*. The differential diagnosis between erythema multiforme exsudativum and pemphigus may be exceedingly difficult, if not impossible, in the early stages and in cases featured by restriction of the process to the oral and other mucous membranes. There is a popular notion that recovery points indubitably to the former disease and death to the latter, but this rule has numerous exceptions, particularly if it is applied to single attacks; temporary "cures" probably occur in pemphigus and fatalities may supervene

On the other hand, there are occasional instances of secondary syphilides presenting, at inception, attributes that simulate erythema multiforme in its broadest sense. Twice I have encountered such eruptions situated chiefly on the abdomen and marked by what appeared to be a pronounced urticarial component (edema?) superimposed on relatively bright-red papules, without accompanying subjective symptoms. It is curious that these two patients had complaints referable to the rectum. Physical examination showed painful fissures in ano, these lesions representing in reality defects in surface continuity of syphilitic chancres. This was recognized in one case after operative intervention was unavailing, and a subsequent Wassermann test was positive (four plus); in the other instance a routine Wassermann test proved to be the revealing sign of an obscure complaint, the patient finally admitting to the practice of pederasty. In these examples there was little likelihood of "erythema of the ninth day" (Milian),<sup>139</sup> as the eruption appeared before the institution of anti-syphilitic treatment. The opinion has been advanced by Ehrmann<sup>140</sup> that erythema multiforme-like lesions in secondary syphilis are not of specific origin, but due to syphilitic tonsillitis which allows multiplication of common bacteria with absorption of their toxins. This interesting belief did not hold in the two cases cited, as sore throat was not a complaint and oral manifestations were absent; and whereas an analogous theory can be held for the rectal lesions, this hypothesis, though reasonable, remains unsubstantiated.

### ETIOLOGY

In 1860 Hebra<sup>9</sup> confessed his ignorance regarding the cause of this disease when he wrote: "These erythemata are often ascribed to catching cold, or to errors in diet, or to mental emotions; but unless the real existence of these conditions can be proved, I regard such expressions as mere commonplaces and shibboleths; and, rather than avail myself of them, I shall confess that the cause of these diseases is altogether unknown to me. It is certain that they do not owe their origin either to the imbibition of alcoholic liquors, or to eating any particular type of food, whether sour, sweet or bitter, whether of animal or vegetable nature." After a lapse of over 75 years substantially little can be added, aside from a mass of suggestive evidence which will be discussed seriatim.

*1. Factor of Infection.* The occurrence of sore throat, fever, joint pains, lymphadenopathy, and other such features, has led observers, with considerable justification, to the conclusion that erythema multiforme exsudativum is an infectious disease. However, numerous attempts to discover the precise causative agent have been fruitless, despite extensive bacteriologic investigations; cultures of blood have generally been sterile. In view of the clinical manifestations some have classed the affection in the category of focal infection, especially when the disease seemed to follow in the wake of a localized focus of infection (for example, fistula from a

erythema multiforme exsudativum, as in Kinnear's paper; and that, to repeat, death does not necessarily mean pemphigus, and recovery does not necessarily mean erythema multiforme exsudativum.

8. *Foot-and-Mouth Disease.* Occasionally, as in several instances under my observation, the oral lesions in erythema multiforme exsudativum may be accompanied by hemorrhagic bullae situated about the nails, and, in such circumstances, the occurrence of foot-and-mouth disease may be suspected. The virus of this affection was apparently first demonstrated in 1920 by Waldmann and Pape who used the guinea pig as the experimental animal. Before this, foot-and-mouth disease could be suspected only on the basis of clinical and epidemiological evidence, and the factor of coincidence was hardly appreciated. In one example of erythema multiforme exsudativum Klauder<sup>28</sup> was unable to demonstrate the virus by the standard procedure of inoculating the serum of vesicles into scarified areas on the plantar surfaces of a guinea pig. Recently, Richter<sup>114</sup> recorded a probable example of foot-and-mouth disease in a man 34 years of age, in whom the affection appeared two days after the ingestion of raw milk, but in view of the atypical clinical features and the atypical results in the inoculation of a guinea pig, it is difficult to be certain of the diagnosis in this case. The present status of the subject has been admirably summarized by Martland<sup>115</sup>: "A differential diagnosis cannot, however, be made with certainty on clinical grounds alone. All suspected cases should be confirmed by infecting a susceptible animal and demonstrating the nature of the virus by cross-immunity tests. Not all cases reported as foot-and-mouth disease have fulfilled these criteria; the majority were recorded before the guinea pig was recognized as an experimental animal in this connection. Many are, therefore, open to doubt, particularly those cases which had cutaneous lesions on areas other than the soles and palms in which the lesions continue to develop for a prolonged period. Foot-and-mouth disease in man is probably a comparatively rare occurrence. Transmission from man to man has not been demonstrated." It is clear, then, that the utmost circumspection is required in the investigator who diagnoses this condition in man, and no case can be regarded as belonging in this category without the direct substantiation of animal experiment and cross-immunity tests.<sup>116</sup>

9. *Dystrophic Epidermolysis Bullosa.* The dystrophic type of epidermolysis bullosa may occasionally simulate erythema multiforme exsudativum. In both there are encountered bullae in the skin and mucous membranes. In the rare instances showing involvement of the ocular structures with the production of "essential shrinkage of the conjunctivae," the differential diagnosis may be most delicate. In general, however, dystrophic epidermolysis bullosa exhibits the following distinguishing features: (1) inception of the process in early childhood; (2) familial occurrence of the disease which is handed down as a recessive character; (3) the concomitance, sooner or later, of dystrophic nail changes; these are practically always associated with alterations in the mucous membranes; (4) the frequent healing with

and in the present state of our knowledge this factor can only be considered as a predisposing cause operating under circumstances that are still nebulous.

On the other hand, Bruce-Jones<sup>147</sup> has recently described a typical example of recurrent erythema multiforme exsudativum, presumably caused by the ingestion of caseinogen, and as this observation seems important, it merits a more detailed analysis. The reasons for Bruce-Jones' belief were: (1) a strongly positive intradermal reaction to this substance; (2) apparent reproduction of the disease following the *fifth* injection of caseinogen given in ascending doses for purposes of desensitization. Two subsequent attacks occurred after the ingestion of chocolate and ice cream, but it is not clear that the author intended to imply that caseinogen was the underlying factor in the production of these recurrences. This interesting observation needs the confirmation of additional such findings in other cases; attempts to reproduce recurrences in this disease *ex juvantibus* must be judged critically, and special care is required in eliminating the factor of spontaneous attacks of the disease due to the unknown agent causing the affection. The need to substantiate the above observation by the collateral method of skin-testing seems advisable. I have not seen an instance of this disease in which the etiology was clarified satisfactorily by means of skin tests, although it must be stated that no systematic efforts were made along these lines.

3. *Factor of Sunlight.* A few observers have recorded examples of erythema multiforme exsudativum in which the condition was apparently initiated by exposure to sun.<sup>55, 148, 149, 150, 151</sup> Ullmann<sup>148</sup> described a case featured by four recurrent attacks of the disease, each one following an intensive exposure to sunlight, and Klausner<sup>149</sup> reported three such instances. Kreibich<sup>150</sup> observed the simultaneous occurrence of erythema iris and erythema solare. These investigators were inclined to attribute a primary etiology to this factor. On the other hand, Polland<sup>55</sup> who cited an instance where the eruption was restricted to the parts exposed to light, believed that such exposure resulted in damage to the vessels, rendering them more susceptible to the unknown causal agent in the disease. Hübner<sup>152</sup> found evidence of an increase in the excretion of porphyrins in a group of 33 cases of erythema multiforme exsudativum; in eight patients there were observed findings that indicated to him probable damage to the liver. Thus far, definite substantiation of these observations is still lacking; moreover, the significance of such findings remains to be evaluated, as the entire subject of porphyrinuria is in a state of flux.

4. *Multiple Etiology.* There is a tendency to invoke the theory of multiple etiology whenever the cause of a disease is unknown, especially if it is one simulated by a host of other affections. Is it justifiable to consider erythema multiforme exsudativum as the counterpart of urticaria, one of the elementary reactions in the skin due to a variety of agents? The data recorded in this paper appear to indicate that this disease is a well-characterized entity in the sense of rheumatic fever as contrasted with "rheuma-

that which is seen in erythema multiforme exsudativum. A classical example illustrating this point is provided by Abramowitz's original report<sup>126</sup> in which "fixed eruptions" were classified under the title of erythema multiforme; several years elapsed before Wise and Abramowitz<sup>127</sup> recognized the etiologic factor (phenolphthalein) in these cases. It may now be said that the appearances presented by this dermatosis are generally so distinctive that the diagnosis of drug rash suggests itself almost at a glance; on the other hand, further observation has revealed similar "fixed eruptions" caused by antipyrin, arsphenamines, veronal and other substances. In other words, additional knowledge has aided in separating these dermatoses from the vague inclusive category of "erythema multiforme."

On the other hand, the enanthems produced by drugs may present almost insurmountable difficulties in the differential diagnosis from erythema multiforme exsudativum, especially in cases featured by the restriction of the lesions to the oral cavity. A cardinal rule, then, is to eliminate the former etiology in all such instances, whenever possible. This requires generally a complete and critically evaluated history in addition to consideration of the features of the enanthem and of the associated collateral aspects. The complexity of the subject, as revealed by study of isolated instances, precludes further discussion in this paper.

*11. Miscellaneous Affections.* In the course of this study there were encountered simulating eruptions in a variety of diseases, such as pneumonia (especially in the stage of resolution), neoplasms (particularly in the deep-seated types subjected to radiotherapy), pernio, "purpura urticans" (?), infectious mononucleosis, periarteritis nodosa, dermatomyositis, etc., etc. On the other hand, examples of erythema multiforme exsudativum were observed in which the clinical features resembled measles, varicella, and infectious mononucleosis, in addition to the other affections considered in previous sections. Other observers have seen what seem to be resembling rashes following vaccination, sensitivity to light, diphtheria, cholera, and trichophytosis among many other conditions, and in the older literature erythema multiforme exsudativum was often confounded with hemorrhagic variola. It is probable, also, that Haverhill fever represents a separate entity, judging on the basis of the available reports.<sup>128</sup>

These eruptions, which are at present designated as "toxic erythemas," deserve renewed study, and it is my belief that future investigations will disclose criteria enabling the observer to recognize the rash with greater precision.

The section will be concluded with a brief consideration of the alleged relation between erythema multiforme exsudativum and the two diseases, tuberculosis and syphilis.

*12. Tuberculosis and Erythema Multiforme Exsudativum.* That eruptions designated roughly as erythema multiforme may be encountered in patients suffering from active tuberculosis seems probable, for neither disease appears to confer an immunity against the other. However, Ramel's

the mouth, and in elderly persons the ordinary precautions against the super-vention of hypostatic bronchopneumonia must be taken.

In summary, the treatment of erythema multiforme exsudativum is at present essentially symptomatic and empirical. In mild cases the use of dangerous drugs is to be deprecated; in severe examples, especially those featured by intense constitutional symptoms and involvement of the mucous membranes, there exists a definite field for the employment of such medication, but the precise evaluation of such therapy must remain for the future.

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a variety of titles,<sup>132</sup> and it seems probable that this syndrome is more common than is indicated by the paucity of reports concerned with it.

13. *Syphilis and Erythema Multiforme Exsudativum*. In 1903 Hoffmann<sup>133</sup> recorded 13 examples of secondary syphilis associated with lesions interpreted as erythema nodosum, erythema multiforme exsudativum, or both; of these, two had erythema multiforme exsudativum alone, while in three other cases this eruption was combined with erythema nodosum. In another publication<sup>39</sup> the present views regarding the alleged syphilitic etiology of erythema nodosum have been discussed, and here it is proposed to confine the remarks to a consideration of the corresponding status of Hebra's erythema multiforme. In some of Hoffmann's patients vesicular and "pustular" lesions were encountered; the rarity of a vesicular component in acquired syphilides need only be mentioned.<sup>134</sup> Subsequently, Lesser<sup>135</sup> opined that the simultaneous appearance of erythema multiforme and erythema nodosum indicated a syphilitic origin, but this has not been substantiated by observations made in the Wassermann-test-era, and it seems likely that this particular view is in need of critical examination. In perusing the data found in the older literature, it appears that there were three sources of difficulty:

1. Confusion of the mucous membrane lesions of erythema multiforme exsudativum with those of syphilis, an occurrence that is by no means rare. Trautmann<sup>136</sup> collected a large number of instances illustrating the point. Of special interest was the remarkable case described by Lau,<sup>137</sup> in which recurrent attacks of erythema multiforme exsudativum were repeatedly treated as syphilis. Nor was this confusion restricted only to the simulating lesions in the mucous membranes, for Besnier and Doyen,<sup>12</sup> Kaposi and others had observed instances of erythema multiforme exsudativum resembling cutaneous syphilis and Grindon "had seen several cases of so-called bullous syphilides presented at medical societies, which upon investigation proved to be herpes iris."
2. Complete reliance on a therapeutic test which in any disease of short duration may lead to "therapeutic fallacies" unless carefully controlled.
3. Insufficient attention directed to the possibility of drug etiology (iodides, etc.), notably in the older reports.
4. To these sources of error may be added a fourth which operates at the present time, namely, the finding of a coincidental positive Wassermann reaction. This I encountered once in a probable example of erythema multiforme exsudativum occurring in a patient with latent syphilis; the rapid disappearance of the rash without the aid of anti-syphilitic treatment argued in favor of these affections being coincidental and unrelated.



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tooth, etc.)<sup>70</sup>; others have assumed a streptococcal etiology on the basis of cursory analogies rather than of actual proof; and it has already been stated that there is little to commend a belief in the tuberculous hypothesis.

On the other hand, a mass of suggestive evidence, chiefly clinical in type, has been gathered in relation to the possibility of a virus infection. These data are based primarily on the association of the disease with lesions of the herpes group of affections. A host of observers have encountered an increased prevalence of erythema multiforme exsudativum during times when herpes zoster was particularly abundant.<sup>55, 141, 142, 143</sup> Lortat-Jacob<sup>144</sup> reported that the bullous fluid obtained from a typical case of hydroa vesiculeux gave a negative cornea test in rabbits. In one instance under my observation the patient showed, in addition to the eruption of erythema multiforme exsudativum, the lesions of both herpes labialis and herpes zoster of the left upper arm with an enlarged, slightly painful gland in the corresponding axilla. Bateman<sup>6</sup> was probably the first to note the concurrence of herpes iris and herpes labialis, while in recent years Forman and Whitwell<sup>145</sup> presented what seem to be cogent observations on the possible relation between these affections. In 12 consecutive instances of erythema multiforme (Hebra) they reported the clinical concomitance of herpes simplex or its occurrence just prior to the appearance of the former eruption. Moreover, they also noted that both diseases tend to recur, that in both sunlight may be a provoking factor, as will be noted later, and that both have a similar seasonal incidence. Considering, however, how common herpes labialis is and in view of a similar seasonal incidence, it is difficult to be certain that their simultaneous appearance in the same patient may not represent coincidence; yet, the number of cases in which Forman and Whitwell observed their concomitance would appear to be so great as to warrant serious consideration of this hypothesis, pending further investigation on the virus etiology. Urbach<sup>146</sup> recorded 20 cases in which herpes labialis preceded erythema exsudativum multiforme by a period of eight days; his experiments in animals, using blood and the contents of vesicles, gave negative results, but these observations seem to provide clinical substantiation of the data presented by Forman and Whitwell.

2. *Factor of Food.* What Hebra said regarding the failure to incriminate food as an etiologic agent in this disease would seem to apply today, though one possible exception will be mentioned shortly. Fordyce observed a case of herpes iris in the mouth, occurring after the eating of lobster; there was a subsequent recurrence, but it is not clear that this followed ingestion of the suspected food. A few isolated instances have been attributed to the intake of fish, oysters, etc., but the evidence presented is not very convincing. Morris and others were of the belief that beer was an occasional cause, and still others observed instances where the eruption was regarded as due to Bacchanalian excesses. It must be admitted, however, that the consumption of alcoholic beverages in various degrees is a practically universal custom,

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tism." In any event, before the concept of multiple etiology is permitted to gain sway, at least *one* cause should be definitely established, as in urticaria, and an effort must be made to distinguish between a predisposing factor (sunlight in herpes simplex) and the actual cause (virus in herpes simplex). In the present state of our knowledge it must be admitted that the etiologic factor or factors in erythema multiforme exsudativum remain to be discovered.

### TREATMENT

In studying erythema multiforme exsudativum several principles illustrating rules in evaluating the results of therapy are exemplified. Owing to the essentially benign course of the average case of this disease, including those showing apparently severe constitutional symptoms, it is not astonishing that numerous remedies have received undue praise. The use of salicylates and related drugs, such as pyramidon and aspirin, is based on the belief in the rheumatic nature of erythema multiforme exsudativum, but the data recorded in a previous section are at variance with this hypothesis; favorable results appear to depend on their coincidental employment in mild cases. A healthy scepticism based on knowledge of the natural course of an affection and its variants should not be confounded with therapeutic nihilism, nor is an attempt at scientific evaluation of a drug inconsistent with its use for purposes of psychic treatment of a patient, especially if the differences between these attitudes are recognized. So far as the average example of this disease is concerned, there is more sophistry than logic in the statement that some cases are helped, others not; nor can undue significance be attached to an alleged shortening of the clinical course of individual examples, for variations in this particular are many and unpredictable. Nevertheless, experimentation with drugs is justifiable under circumstances to be defined shortly.

Among the drugs recently advocated in the treatment of this disease are germanin and sulphanilamide. In the section on prognosis it was stated that erythema multiforme exsudativum becomes a dangerous disease chiefly when the mucous membranes are affected, and it is in these cases that a more precise idea regarding the value of medication will be learned in respect to (1) the prevention of complications, such as bronchopneumonia and ocular lesions; (2) the shortening of the clinical course. It is, of course, understood that some attempt must be made to gain more accurate information relative to control cases of similar severity. The first essential, then, is to use the medication in those instances exemplifying a severe grade of disease. There is a fundamental objection against the employment of germanin in mild cases of the affection, for it is not an innocuous drug; sulphanilamide may be used, perhaps, with greater impunity, though the patient bears careful watching nonetheless. In all instances in which the oral mucous membrane is involved it is essential that careful attention be paid to the state of

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If the periodicity of these pains is observed, the diagnosis of coronary thrombosis can be made and will usually be substantiated by later positive evidence. This pain syndrome has proved invaluable in ruling out the presence of extracardiac anginas due to lesions above or below the diaphragm, such as acute gall-bladder disease, ruptured peptic ulcer, acute pancreatitis, intestinal obstruction, acute pneumothorax and pulmonary embolism or infarct.

The following charts describe various types of pain quality in coronary thrombosis. Each chart attempts to represent graphically the pain course in an actual patient who was observed in an attack. The cases chosen for analysis are typical of many other similar ones observed in various patients in ward, consultation, and private practice over a period of 15 years.

For comparative purpose, pain intensity is depicted as 0, 25 per cent, 50 per cent, 75 per cent, and 100 per cent. As there is no known accurate measure for pain intensity, these percentages are based on the patients' reactions, such as restlessness, groans, cries, facial expressions of agony, and general state of shock. Time intervals are spaced to represent the passing of five minutes. The letter P represents the time duration of pain. The height of P in relation to the rest of the chart depicts the intensity of the pain. The letter R represents relief and the duration of the relief. The amount of relief is depicted by the amount of fall from the pain level.

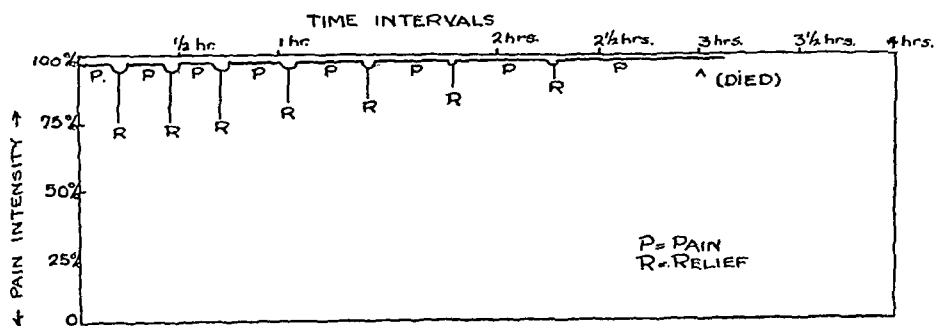


FIG. 1. Very severe attack with fatal outcome.

#### CASE REPORTS

*Case 1.* Male, 42 years old, was seized with sudden precordial pains. A diagnosis of "cold in the chest" was made by the first physician called. When seen by his own physician half an hour later, the patient's condition was diagnosed as coronary thrombosis. When examined by me, one hour and a half after the attack began, the patient was in shock, with the typical picture of acute coronary failure: profuse sweating, anxious pained expression, ashen skin, systolic blood pressure 0, pulse imperceptible. The diagnosis of this case was not confirmed by electrocardiograms or autopsy, but in view of a past history of angina pectoris and the subsequent findings, it is felt that the diagnosis was justifiable.

#### ANALYSIS

The chart shows the intensity of the pain in this patient to have been at the 100 per cent level. When first seen the pain paroxysms lasted about 10

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of the relief periods increased progressively so that relief to the 75 per cent level of pain intensity in the first hour became almost complete relief in the fourth hour.

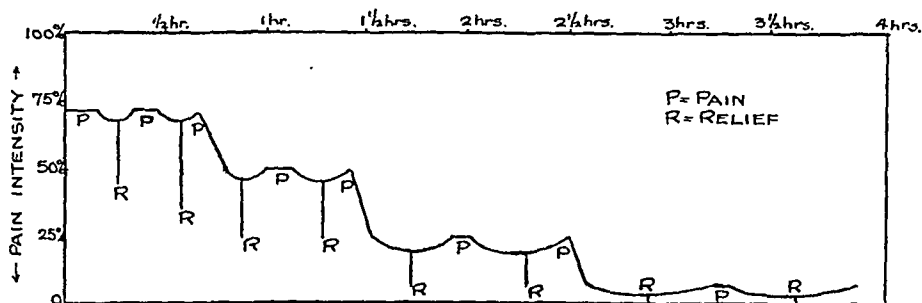


FIG. 3. Moderately severe attack with recovery.

*Case 3.* Forty-year-old male with no past history of discomfort. Pain was confined to the epigastrium; there was some vomiting; and at the time there was a question of gall-bladder disease. The patient was treated for coronary thrombosis because of recurrent pains and drop in blood pressure, and was in bed about six weeks. Recovery was uneventful, until sudden death about six months later after climbing five flights of stairs following a heavy meal. Coronary thrombosis in this case was proved by positive electrocardiographic findings.

### ANALYSIS

In this patient the pain level was at the 75 per cent mark. He was not greatly shocked. The pain paroxysms were short, the relief intervals became quite long after one hour and a half, and the patient went on to recovery from the immediate attack.

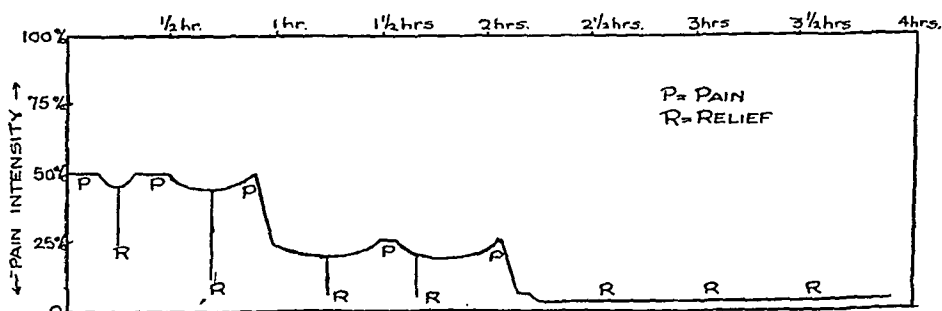


FIG. 4. Moderate attack with recovery.

*Case 4.* Male, aged 51. There was a history of substernal attacks of oppression on exertion for a number of months, and also of dyspnea and tiredness. The patient was seized suddenly with substernal discomfort while in bed at night. Coronary thrombosis was proved by electrocardiographic evidence and such clinical findings as fever, leukocytosis, increased sedimentation rate, and pericardial friction rub. The patient has had no recurrences, no evidence of congestive failure, and very few attacks of angina pectoris since his coronary thrombosis.

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sternal ache. In the twenty-second hour there was a sudden sharp rise in pain from 5 per cent to 100 per cent intensity. It remained at this high level, little influenced by morphine, until the thirty-sixth hour, at which time the patient expired.

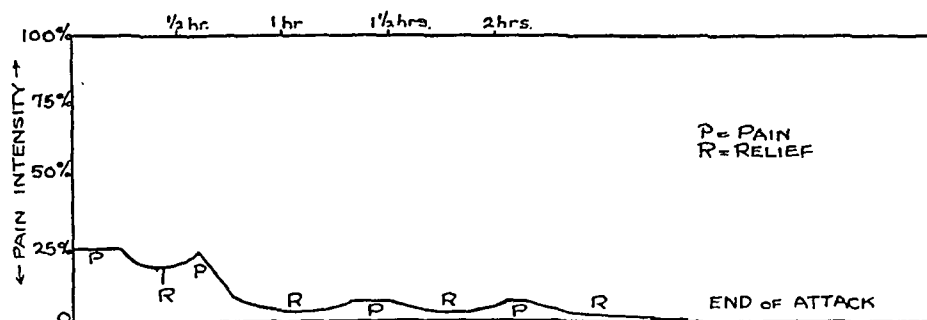


FIG. 6. Atypical attack with recovery.

*Case 6.* Male, aged 60. There was no history of angina. The patient complained of sudden epigastric discomfort following a heavy dinner, and of nausea, without vomiting. This discomfort produced a sense of 'being full of gas' rather than of having pain. The patient was greatly relieved after belching. There had been four paroxysms of this discomfort, on the basis of which a diagnosis of coronary thrombosis was made and proved by electrocardiograms. The patient remained in bed four weeks after finally being convinced that he was not suffering from indigestion. He made an uneventful recovery.

### ANALYSIS

The intensity of the pain was at the 25 per cent level. There were two paroxysms in the first hour, lasting respectively 15 and 12 minutes. In the second hour the paroxysms lasted 10 and 5 minutes, and were on a 5 to 10 per cent intensity level. Complete relief came at the end of two and one-half hours.

### COMMENT

The six cases chosen as examples typifying rhythmical pain run the gamut from very mild to most severe attacks. A study of a large series of cases will present variations as numerous as the cases themselves. In some the rhythmical sequences of pain and relief are absolutely regular for a few hours; in others there is no regularity. The intensity and length of the pain paroxysms may be increased suddenly following a preceding decrease. The recurrent pain episodes are sometimes unrecognizable in those very severe attacks in which the patient is prostrated. The pain syndrome which has been described will be recognized in most cases of coronary thrombosis if the physician takes the time and pains to observe his patient closely and continually. It must be emphasized, however, that absence of this syndrome should not make for a negative diagnosis in the presence of other positive findings. Early negative electrocardiograms in questionable cases

## A NEW OBSERVATION HELPFUL IN THE DIAGNOSIS OF CORONARY THROMBOSIS \*

By PETER J. STEINCROHN, M.D., *Hartford, Connecticut*

THE various descriptions of coronary thrombosis pain in the literature may be summarized as follows: The pain results from anoxemia of the cardiac musculature secondary to decreased blood supply; it is intense, unbearable, and amenable only to large doses of morphine; its location is usually under the lower sternum or in the epigastric region; the pain may be referred, among other locations, to the arms or jaw; the pain is continuous and is accompanied by varying degrees of shock.

In studying patients during attacks of coronary thrombosis, I have observed a pain syndrome which has not been mentioned or stressed in the literature on the subject.

The purpose of this article is to describe this syndrome. It has proved valuable in the diagnosis of obscure cases of coronary thrombosis, particularly in those patients in whom suspicions of this disease process could not be confirmed because of negative *early* electrocardiograms.

In evaluating substernal or epigastric pain which is possibly of coronary origin, it is important to consider carefully its quality. One must ask: Is the pain momentary or continuous? Is it periodic or rhythmical? Are its recurring intervals decreasing or increasing in number and in intensity of discomfort?

I have found the outstanding characteristic of pain in coronary thrombosis to be its rhythm and periodicity. This holds true for indefinite attacks and also for those in which the pain and shock are so prominent that the diagnosis is unquestioned. The pain comes and goes in cycles. It is unbearable for a variable short period of time and then subsides for a period equal to or many times longer than the actual pain. Then it returns again to be followed by another pain-lessened or pain-free interval. This cycle is usually repeated a number of times.

To establish the presence of periodic pains the patient must be observed closely for at least 15 minutes to half an hour, a longer or shorter period of time depending upon the intensity of the pain and on how soon after the beginning of the attack the patient is seen. Sometimes the return of pain is heralded only by increased restlessness, at other times by an anxious and painful expression accompanied by loud or subdued groans. These symptoms disappear with the return of the pain-lessened interval.

When the patient is first seen in an attack morphine should not be withheld. The administration of this drug will not obscure the diagnosis. If the above-mentioned pains are present, they will continue to recur and remain recognizable before the morphine exerts full effect.

\* Received for publication December 12, 1938.

## LIVING WITH THE WEATHER \*

By F. M. POTTENGER, M.D., F.A.C.P., *Monrovia, California*

### SHIFT FROM BACTERIOLOGIC TO PHYSIOLOGIC INTEREST IN MEDICINE

WHEN bacteriology supplied the cause of infectious diseases it gave definite direction to the development of medicine, both preventive and curative, for several decades. By learning the cause and the method of transmission, preventive measures were instituted more or less simultaneously throughout the world. The effects of these were shown everywhere by a reduction in morbidity and mortality. As a result, in the United States the general death rate dropped from about 18 per 1,000 of the population 50 years ago, to about 11 today. Since most of the preventive measures have been particularly operative in case of diseases which affect the young, those who formerly would have died during the first two or three decades of life now live on to mature years or even old age.

Whereas 50 years ago about 95 per cent of illness was acute, today 75 per cent of it is chronic. This shift in the nature of illness has changed medical thought and practice; and physicians are now devoting more of their study to problems of development, the chronic infections, degenerative and deficiency diseases, and to disturbances of a functional nature.

The change in type of disease calls for a more intensive study of the patient; and physiology now becomes of greater importance than bacteriology in providing an understanding of present-day medical problems. As physiologic knowledge increases, its contribution to the understanding of all diseases becomes more and more important. Even defense against infections is a physiologic process; and the scientific treatment of all diseases follows physiologic principles.

In our study of man as a physiologic being we are impressed with the fact that he is influenced by many stimuli of both a physical and psychic nature. They may originate either outside the body or within. Internal stimuli may be set free by such processes as the digestion of food within the gastrointestinal tract; by parenteral digestion of proteins; by secretions of various kinds; by bacterial toxins, or other toxic substances which arise within the body; or, by stimuli of emotional origin. Stimuli which arise in the external environment are also of many types. Among those which most frequently cause helpful stimulation, on the one hand, or stresses and strains which unbalance the physiologic mechanism, on the other hand, are the atmospheric forces in the midst of which we live, but to which we fail to assign a position of importance.

\* Read at the Twenty-third Annual Clinical Session of the American College of Physicians, New Orleans, March 30, 1939.

minutes with the pain-lesened intervals of about five minutes. In the relief intervals the pain fell only to about the 75 per cent level. At the end of an hour it will be observed that the P intervals became longer and remained on the 100 per cent intensity level. On the other hand, the R intervals became shorter, descended less and less, so that even in the pain-lesened intervals the relief was not as marked as at the beginning of the attack. At the end of two hours (about three and a half hours after the onset) of observation the pain was practically continuous and the patient expired about one hour after the onset of this steady pain. One and one-half grains of morphine sulphate were given without any decrease in the intensity of the pain. This case is reviewed briefly to indicate that these pain and relief intervals are also present in unmistakable attacks.

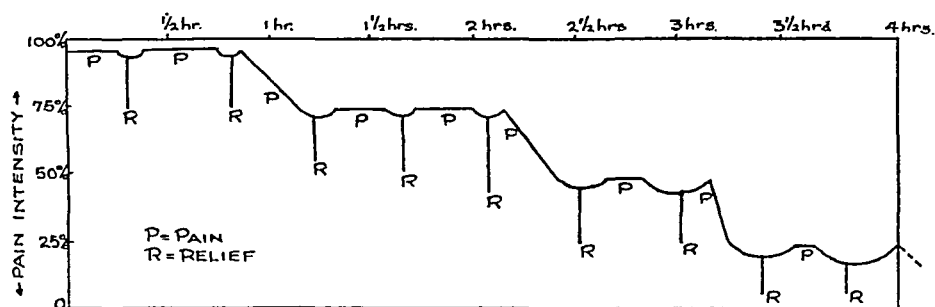


FIG. 2. Very severe attack with recovery.

*Case 2.* Male, aged 54 at time of attack in 1930. An electrocardiogram was taken at 2 p.m. due to a history suggestive of angina pectoris. Ten hours later, following heavy exertion, this patient suffered the severest attack of substernal pain, with recovery, that I have ever seen. He was pulseless, moribund, and terribly shocked; blood pressure was zero in the arm. A very slow pulse with many dropped beats first became palpable in about half an hour. His systolic blood pressure rose to 50 at the end of four hours. He remained in bed three months due to a complicating thrombophlebitis in each leg. He is alive today, probably due to the fact that the complicating phlebitis has greatly limited his activities. The electrocardiogram, taken 10 hours before his attack of coronary thrombosis, showed a prominent S-wave in Lead II. It was otherwise negative. After the attack the electrocardiograms showed typical changes in the S T intervals.

### ANALYSIS

The intensity of the pain in the first hour was 100 per cent. It fell to 75 per cent in the second hour, 50 per cent in the third hour, 25 per cent in the fourth, from which point the pain gradually cleared up. In the first two and a half hours the pain paroxysms lasted 15 to 25 minutes, after which time they varied between five and 10 minutes, and disappeared at the beginning of the fourth hour to be replaced by a low grade aching sensation under the sternum.

The periods of relief, which lasted eight to 10 minutes in the first two hours, widened out to 15 and 25 minutes in the next two hours. The depth

### PHYSIOLOGIC EFFECTS OF DIFFERENT METEOROLOGIC FORCES

Some of the earliest studies in this country were those of Huntington.<sup>1</sup> He stressed the effects of temperature and humidity. He made a study of the daily work of three or four thousand mill operatives in New England, and the Southern States, also of 1700 students at Annapolis and West Point. He found that the daily variation of temperature in which the mean maximum was about 64° F. and the mean minimum was about 38° F. was the most favorable for productive effort. Of course, humidity, wind movement and other forces are modifying factors. Another important factor was the changeableness from day to day. He found that neither too great changes

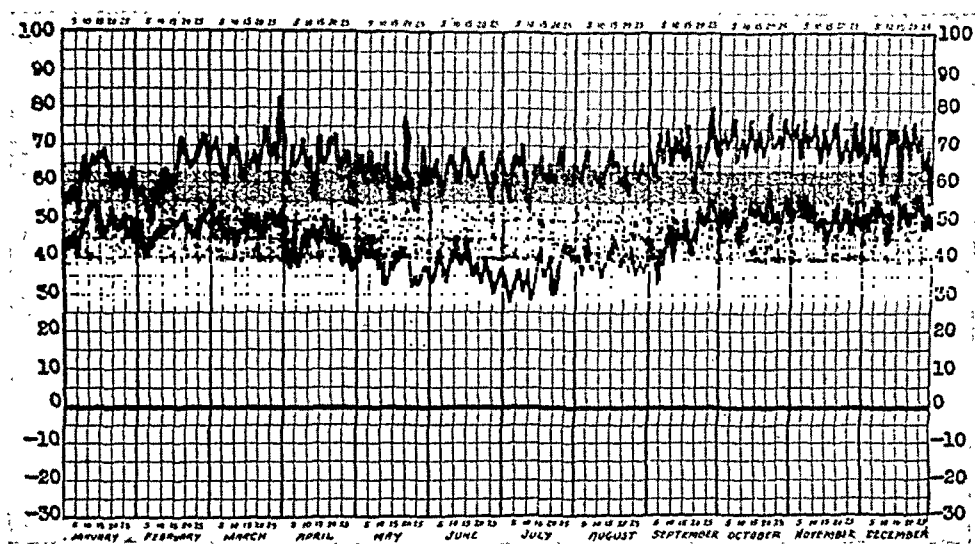


FIG. 1. Daily maximum and minimum temperatures, Sucre, Bolivia, 1923 (Mills).

nor monotony were favorable for best physical or mental accomplishment, but that moderate variability added to climatic efficiency. He called attention to the fact that in the past, atmospheric features similar to those which he described as optimal were present at the time that many nations reached the pinnacle of their civilization.

Petersen,<sup>2</sup> in his epoch-making observations, has studied the effects of the various meteorologic forces upon the many physiologic reactions of normal men with different constitutional peculiarities, as well as those suffering from different diseases.

Likewise he has endeavored to determine the force which affects man most and stresses particularly barometric change which is most marked at times of storm.

Mills<sup>3, 4</sup> has studied the demands made by daily variations in temperature on people living in different climates. He has particularly noted the effects according to the manner in which they depart from the optimum temperature variation established by Huntington. This he illustrates by the following charts. In each figure the stippled band represents Huntington's optimum

## ANALYSIS

This patient did not look very ill when first seen. His pain level was at the 50 per cent mark. Although his first attack of pain lasted 15 minutes, the relief interval lasted 10 minutes, during which time the pain disappeared entirely. The next pain paroxysm lasted five minutes, followed by freedom from pain which lasted 25 minutes. There followed two short pain paroxysms of lessened intensity. Relief set in at the one and one-half hour period, following which there was no pain recurrence.

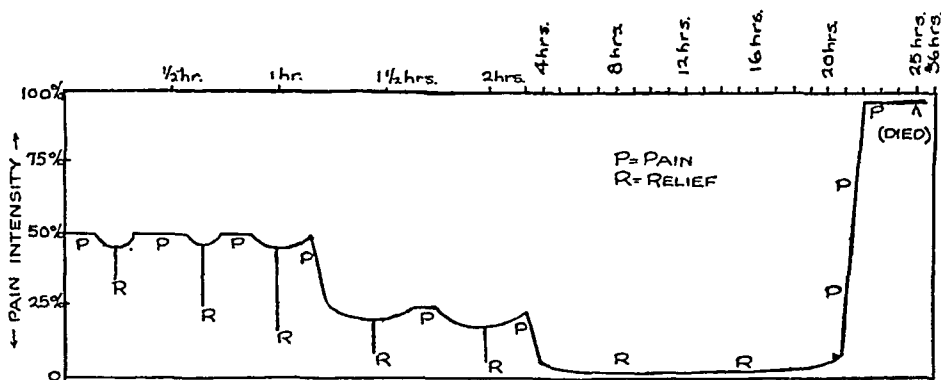


FIG. 5. Moderate attack with fatal outcome.

*Case 5.* Ninety-year-old male, who was three times a widower, and who had married a fourth time at the age of 82. He had been well except for occasional slight attacks of angina pectoris which did not prevent him from travelling and being quite active. His regular physician, who had seen him a few months before this attack, had made a diagnosis of arteriosclerotic heart disease—coronary sclerosis—angina pectoris—normal rhythm—Class 11A.

I was called to see this patient for the first time about half an hour after the attack began. It was a moderate attack. He did well until the next day when severe substernal pain returned and continued until death, 36 hours after the beginning of the attack.

The patient's own physician refused to concur in the diagnosis, which had been made only on the basis of the periodic pains suffered by the patient at the beginning of the attack. This physician diagnosed the condition as acute pneumothorax. Despite good heart sounds, normal blood pressure, and negative electrocardiographic findings (taken 30 hours after the onset), the diagnosis of coronary thrombosis was adhered to. An electrocardiogram taken half an hour before death (six hours after the first tracing) showed positive changes indicative of coronary thrombosis.

This case is enlightening, as it proves the value of correctly interpreting rhythmical pains when considering the possibility of coronary thrombosis.

## ANALYSIS

The pain remained at the 50 per cent level for the first hour. Each period of relief became deeper and longer. During the second hour the pain remained at the 25 per cent level, and the paroxysms lasted only five minutes. From the fourth hour to the twenty-second hour (observations of the nurses) there was complete relief from pain except for slight sub-



and is best able to maintain health. The temperature with great daily and seasonal variations makes extraordinary demands upon man's adaptive mechanism, and may precipitate disease in those with low resistance. On the other hand, it stimulates the strong to withstand unusual effort and raises their resistance to disease. Those who live in monotonous non-stimulating climates do not suffer from diseases which are produced by stress, such as hypertension, hyperthyroidism and diabetes, to the same extent as those who live in more rigorous climates.

That the prevailing diseases from which people suffer in these various climates would differ is to be expected. So is it reasonable that the same disease might affect people of these varying climates differently. It is well known that the people of the tropics do not show the same resistance to tuberculosis that is shown by those who live in the temperate zone, also that the less resistant patients do not withstand the rigors of Northern winters as well as those who are more vigorous.

Appendicitis is more common in the more stormy portions of the United States than in the warmer, milder portions, but the mortality is greater in the latter probably because of the lack of the invigorating meteorologic forces which increase the patient's ability to withstand.

The rigors of the North increase the incidence of such metabolic disorders as thyroid disease, diabetes and pernicious anemia, as shown by Petersen and Mills.

### STORMS

All atmospheric forces are more turbulent at time of storms, and physiologic mechanisms are called upon to make greater compensation. Storms, in the meaning here used, denote the condition in which the air, warmed in the tropics, is sent Northward producing a high pressure area which meets the cold air from the Arctic regions coursing Southward, thereby producing a low pressure area. The struggle between these air masses is productive of a turbulence which is designated as a storm. The barometric pressure changes; temperature and humidity are altered; air currents vary, and electric potential shifts.

The major factors which determine the direction and course of these air masses are the masses of water and land, and the contour of the land, as modified by mountains, river valleys and plains. These being fixed and definite, the storm tracks are accordingly quite definite. The paths for the storms on the American continent descend from the North Pacific through the Mackenzie Basin or from Alberta and enter the Northwestern part of the United States, then they course Southward along the Eastern slope of the Rockies until they are deflected Eastward and Northward to pass over the Great Lake region and down the St. Lawrence Valley. Many of them pass farther Southward over the Mississippi Valley, but the main tracks keep well to the North. The Great Lake region has the reputation of being the stormiest area in the world. Northern Europe, on account of the land

should not influence the physician against a diagnosis of coronary thrombosis if he has observed at least three recurrent pain paroxysms. The patient should not be discharged as being free from this disease unless serial electrocardiograms are negative and other evidence is lacking.

The cause for the recurring pains is difficult to prove. Theoretically, it might be explained on the basis of the changing level of anoxemia which is dependent on the adjustments which the cardiac circulation is called on to make in the first few hours following the immediate shock of the attack.

The pain of an attack of coronary thrombosis may be compared with the pain of a number of successive attacks of angina pectoris which follow one another closely. The pain and rest intervals in coronary thrombosis differ from these only in that the pains are more severe in the former and are unrelated to exertion. When viewed in the light of the similar underlying pathology of the two conditions it seems natural to compare the pains of the coronary thrombosis patient who is resting with those of the angina patient who is exerting himself. Both conditions are usually the result of an underlying coronary sclerosis, and each could well be listed under the heading of acute coronary failure.

In attempting to describe the rhythmical pains of coronary thrombosis I have referred to them as labor pains of the heart. This comparison has been employed after due consideration, because no other type of rhythmical pain in medicine is as commonly known to every physician as the physiological labor pains of the woman at term. The similarity between these pains and those of coronary thrombosis is often striking, and of great prognostic value. That patient usually succumbs who has periodic substernal or epigastric pains, which resemble the uterine pains of the pregnant woman just before delivery. Here the bouts of pain become longer and the rest intervals shorter, until such time as there is no pain-free interval. If, however, the cardiac pains resemble those of uterine inertia, i.e., strong at first but gradually becoming weaker and farther apart, until they stop, the patient usually recovers from the immediate attack.

#### SUMMARY AND CONCLUSIONS

1. Descriptions of coronary thrombosis pain in the literature do not mention or stress the importance of evaluating the quality of this pain.
2. The outstanding characteristic of this pain is its rhythm and periodicity.
3. The patient must be observed carefully before the presence of these characteristics can be determined.
4. If the periodicity of these pains is observed, the diagnosis can be made and will be substantiated by later positive evidence.
5. An analysis of six patients has been made to describe this pain syndrome.

## EFFECT OF METEOROLOGIC FORCES ON DISEASE

Ill effects, too, may be shown in observing the clinical course of a disease, such as tuberculosis. Hemoptysis, pain, insomnia, pleural effusion, metastatic spread, and exacerbations appear seasonally; and also appear in multiples at the same season, being precipitated by storms. The season which shows most exacerbations and most spread of the disease is the late winter and early spring, after the patient has been long subjected to the stresses of winter weather. A period of lesser severity is shown in the fall at the approach of winter.

There is five or six times as much acute miliary tuberculosis in the spring as there is in midsummer. The same is true of tuberculous meningitis among children. This is shown in figure 4, from Engel and von Pirquet.

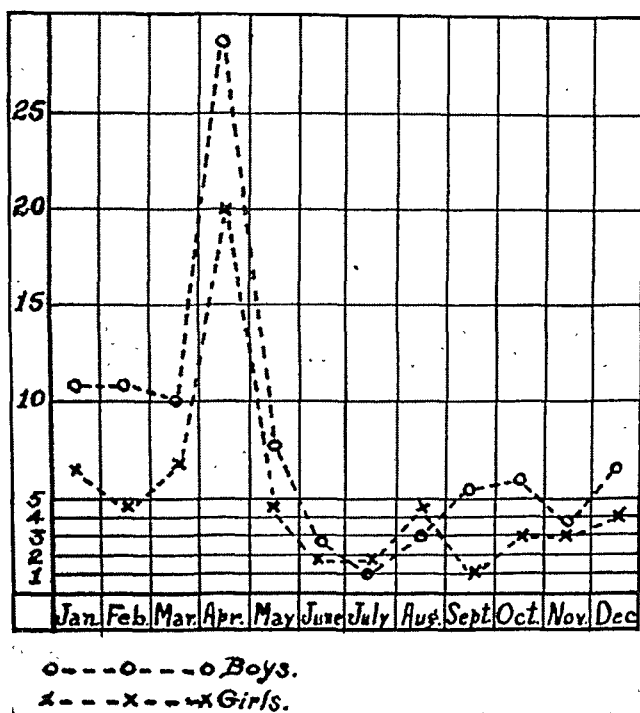


FIG. 4. The relative percentage of cases of tuberculous meningitis in children for the different months of the year, showing the enormous increase in the spring months and low percentage in summer (Engel and Pirquet: *Handbuch der Kindertuberkulose*, 1930, i, 531).

For many years we have observed that there is a seasonal increase in the number of severe cases of tuberculosis at the end of winter and early spring. Moreover, we have noticed that storms hasten death in patients who are quite ill.

Figure 5, from the 1937 Health Report for the City of Sheffield, England, shows numerous curves, but I wish to call particular attention to the atmospheric temperature curve; the death rate from all diseases, that from heart disease, and tuberculosis and other respiratory infections. It will be

## MAN'S PHYSIOLOGIC ADAPTATION TO METEOROLOGIC FORCES

The human body is a receptor mechanism which receives and transforms stimuli of various kinds and varied intensity into action. It has a remarkable power of adaptation. One who is physiologically stable has the ability to adjust to heat equal to that in the tropics and to cold equal to that in the Arctic; to an atmosphere saturated or one almost devoid of moisture; to a gentle zephyr or to a wind movement of hurricane proportions; to a low or high barometric pressure; to light of great or of little intensity; and to varying degrees of electric potential.

Atmospheric forces are rhythmic in nature, varying daily, seasonally, and cyclically. They also vary geographically. The forces may be mild or turbulent. The varying reactions with which man responds may depend on constitutional or acquired differences. He varies in reaction in illness and in health, and at different age periods. He may possess organs with varying susceptibility. Some men might be particularly subject to diseases of the respiratory tract; others to diseases of the cardiovascular, renal, gastrointestinal, endocrine or blood systems. From this it can be seen that there are many variables which will determine or modify the manner in which man's physiologic mechanism will react to the atmospheric forces; and it is evident that he does not adapt so readily or so completely when ill as when well.

There is a difference in opinion as to what particular atmospheric force is most potent in causing changes in the body's reaction. It may be, as far as present knowledge is able to determine, some one or some combination of several forces. The action of any force which produces stimulation is shown in changes in oxidation. This may be confined locally or expressed widely. The stress falls heaviest upon tissues which are the seat of pathologic change because the cells which are involved have altered reactivity. A hyperactive cell has its electric reactivity altered and its permeability increased. So, strong stimuli may produce effects which are purely physiologic, or effects which fall outside of normal physiologic limits and result in dysfunction or disease. If disease is already present in a quiescent state, they may reactivate it. They may increase activity if the process is already active, or they may even cause death of the patient.

The usual effects of atmospheric forces of normal intensity impinging upon the body of the average man in health fall within the point of normal physiologic stimulation. However, at times of storm the stress is multiplied many times and may produce harmful effects. Thus we live and enjoy, become ill, improve or fail to improve and die with the weather.

If we attempt to explain how these effects are produced, we will find difficulty in establishing the cause with absolute definiteness. However, careful observation of groups of people will make it possible for the observer to satisfy himself beyond doubt that people in general are meteorologically influenced in their reactions, and that different individuals react with different degrees of intensity to the same stimulus.

of the patients show slight clinical disturbance. The most marked atmospheric changes came on May 4 and 5, when there was a drop in the barometer, and elevation of temperature and a continuation of a high humidity which was preceded by a rain on the first and second of the month.

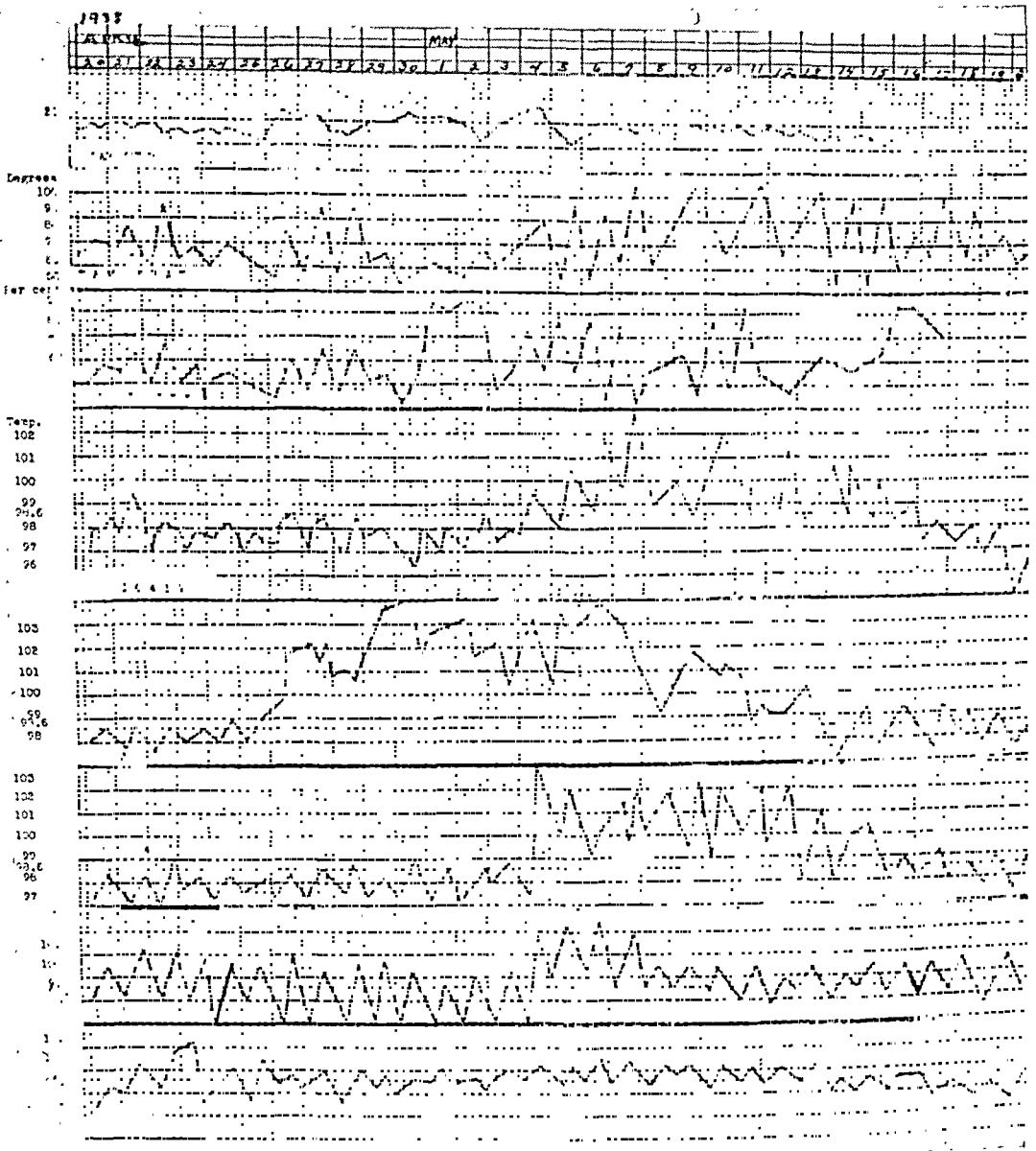


FIG. 6. Relation of symptoms and complications in tuberculous patients to meteorologic factors.

It will be noted that patient 10419 showed the beginning of an active tuberculous process which lasted two weeks. Patient 10838 was suffering from a complicating pleurisy with effusion. The temperature had attained a maximum and was receding, but showed the beginning of a second eleva-

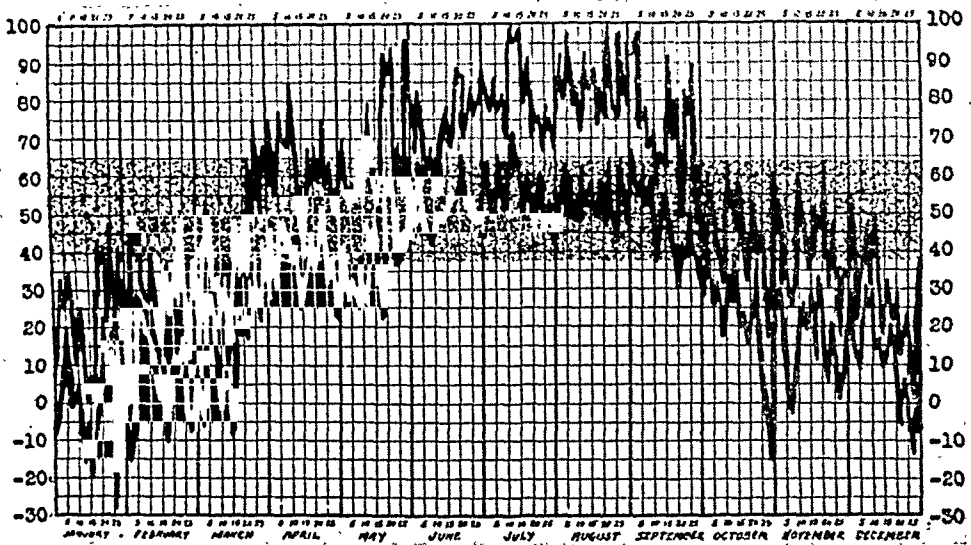


FIG. 2. Daily maximum and minimum temperatures, Bismarck, North Dakota, 1925 (Mills).

daily variation. Figure 1 represents a climate in which the diurnal variation in temperature for most of the year falls within this optimum, hence is a climate which favors productive effort throughout the year. Figure 2 is one in which both daily and seasonal variations show wide swings calling upon the individual to make enormous daily and seasonal compensation. Such a climate is rigorous and calls for adaptation which the less vigorous may not be able to make. Figure 3 is a monotonous climate such as is found in the tropics where the temperatures, both daily and seasonal, fall outside and above the optimal limits.

Under conditions of optimal temperature man is able to accomplish most,

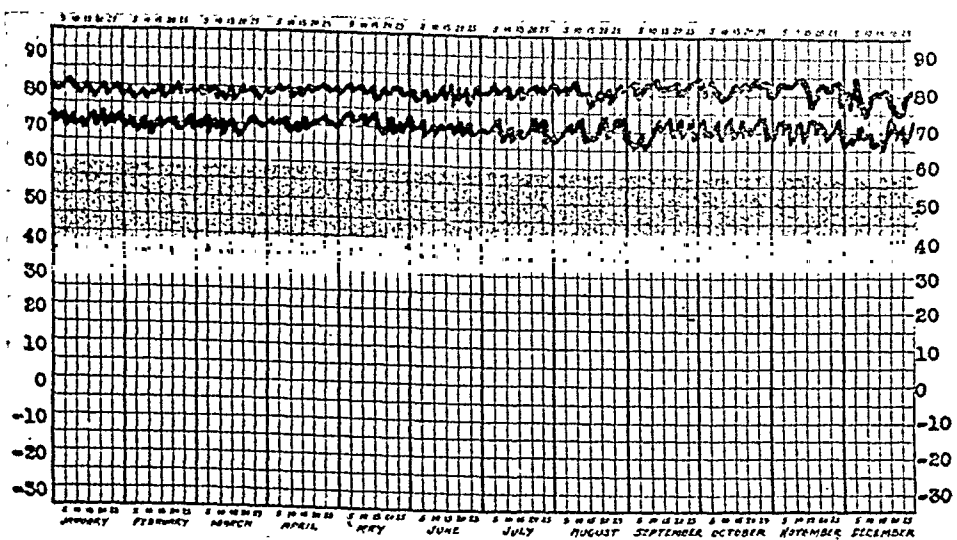


FIG. 3. Daily maximum and minimum temperatures, Georgetown, British Guiana, 1923 (Mills).

reactions may result in well-being and conditions of health; in conditions of malfunction and disease; and eventually in healing with restoration to health; or in death.

Man lives happily, he becomes ill, and recovers or dies with the weather.

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and water topography, escapes much of the storminess which dominates the Northern part of the United States. Excessive storminess is accountable for the rigorous, variable climate in the Northern portion of the United States, and calls for a hardy people.

If one would comprehend the possible sum total of effects produced on man by atmospheric forces, he must consider both the daily and cyclical changes which occur in air masses; and that all differences in temperature, humidity, velocity, changes in ionization and electric potential, and differences in light transmissibility require adjustment. Think of the adaptation that is required of man to adjust to air movement when it attains a velocity of cyclone proportions, or of the rapid changes in barometric pressure at the time of tropical storms!

#### HOW ATMOSPHERIC FORCES PRODUCE EFFECTS

These atmospheric forces produce their effects through all of the physiologic mechanisms of the body, nerves, hormones and body electrolytes. They act primarily upon the skin with its rich supply of sensory nerves. These transfer the stimuli centralward where they are transferred to motor mechanisms, usually of the vegetative system, to be distributed to the various parts of the body for action. Some of these forces, too, produce psychic effects which may result in either normal or pathologic stimulation of the physiologic mechanisms.

The fact that the stimuli act upon all of the physiologic mechanisms is illustrated by the effects of heat stroke in which the loss of sodium, the deficiency of the adrenals, and reduced sympathetic stimulation each make up a part of the picture.

Meteorologic forces may bring about general physiologic response or a response limited to some particular organ. The latter may be the case when the organ is the seat of disease which prevents full and free physiologic adaptation.

There is nothing specific in these meteorologic forces. They produce effects similar to those caused by other stimuli which produce general physiologic effects. This may be illustrated by pulmonary and pleural pain. Patients who have had pulmonary tuberculosis with involvement of the pleura may, long after the disease ceases to be active, suffer from pains in those sensory nerves which were reflexly influenced at the time of the acuteness of the process. Such pain is frequently brought on at the time of storms. However, it may come with other forces which act widely upon the physiologic mechanism such as emotional stress, infections, tiring, and menstruation. The same is true of other types of visceral pain. It has long been recognized that the arthritic is sensitive to weather change.

These general physiologic stimuli are by no means always harmful. Mild meteorologic effects produce normal body activity and aid in restoring health when damaged. This is shown in the effects of favorable climatic influences and pleasing emotions upon people.



ease and the etiologic agent in 1882 he dealt mainly with necropsy material in which the bacillus in question was a secondary invader. He believed that it was the chief etiological agent in lobar pneumonia. In the next few years the work of Sternberg, Frankel, and Talomon in studying the pneumococcus led them to believe that the Friedländer bacillus was never the primary cause of pneumonia. It was Weichselbaum,<sup>7</sup> in 1886, who first stated the truth of the situation, that the Friedländer bacillus is the primary etiological agent in a small but definite percentage of cases. Howard<sup>8</sup> agreed, but set the incidence at 5 per cent. The result of the conflict in opinions of these early investigators, coupled with errors in bacteriological technic and classification of organisms and changing nomenclatures, was that early statistics on the bacteriology of respiratory diseases and the bacteriological data on most case reports were worth very little. Not until about 1905 were bacteriological technic and classification so standardized that statistics commenced to have real significance.

#### INCIDENCE RELATIVE TO ALL PRIMARY PNEUMONIAS

In attempting to get a true idea of the percentage of pneumonias due primarily to the Friedländer bacillus in recent years one finds only four series suitable for analysis. These four are: (a) the only ones large enough to be statistically significant; (b) reported by men of unquestioned ability; (c) reported from records of hospitals whose diagnostic and laboratory standards are pre-eminent. Curiously enough all of the aforementioned cases are from New York or its vicinity. The incidences in the individual series are 0.4 per cent, 0.62 per cent, 0.64 per cent, and 1.08 per cent. In the total number of 11,248 pneumonias 86 cases of primary Friedländer pneumonia were found, a relative incidence of 0.76 per cent.

TABLE I

Author	Locality	Year Reported	Years Covered in Survey	Total Number of Pneumonias	Number of Friedländer Pneumonias	% of Friedländer Pneumonias
Avery <sup>9</sup> Chickering Cole Dochez Cecil <sup>10</sup>	Rockefeller Institute	1917	Not Stated	480	3	0.62%
Baldwin Larsen	New York	1927	Not Stated	2,000	8	0.4%
Solomon <sup>3</sup>	Bellevue Hosp. N. Y.	1937	1920-1937	5,000	32	0.64%
Bullowa <sup>11</sup>	Haarlem Hosp. N. Y.	1937	1929-1936	3,768	41	1.08%
Total				11,248	86	0.76%

There were several large pneumonia series reported from Europe, but these lacked specific data on Friedländer bacillus infections. Once the pneumococcus was excluded as the etiologic agent the investigation of the remaining cases was not pursued by the laboratories, either because of lack of interest or finances. The above figure, 0.76 per cent of all pneumonias, is as accurate as the available data allow. A few investigators have reported a higher incidence based on

noted that the preponderant number of deaths occur in the colder months. These are not only the months of storm, but the months in which the effects of storms are cumulative, so that after a succession of severe stimulations the patient's resistance is lowered and easily overcome. The death rates in many of our large Northern cities have been analyzed by Huntington, Peter-

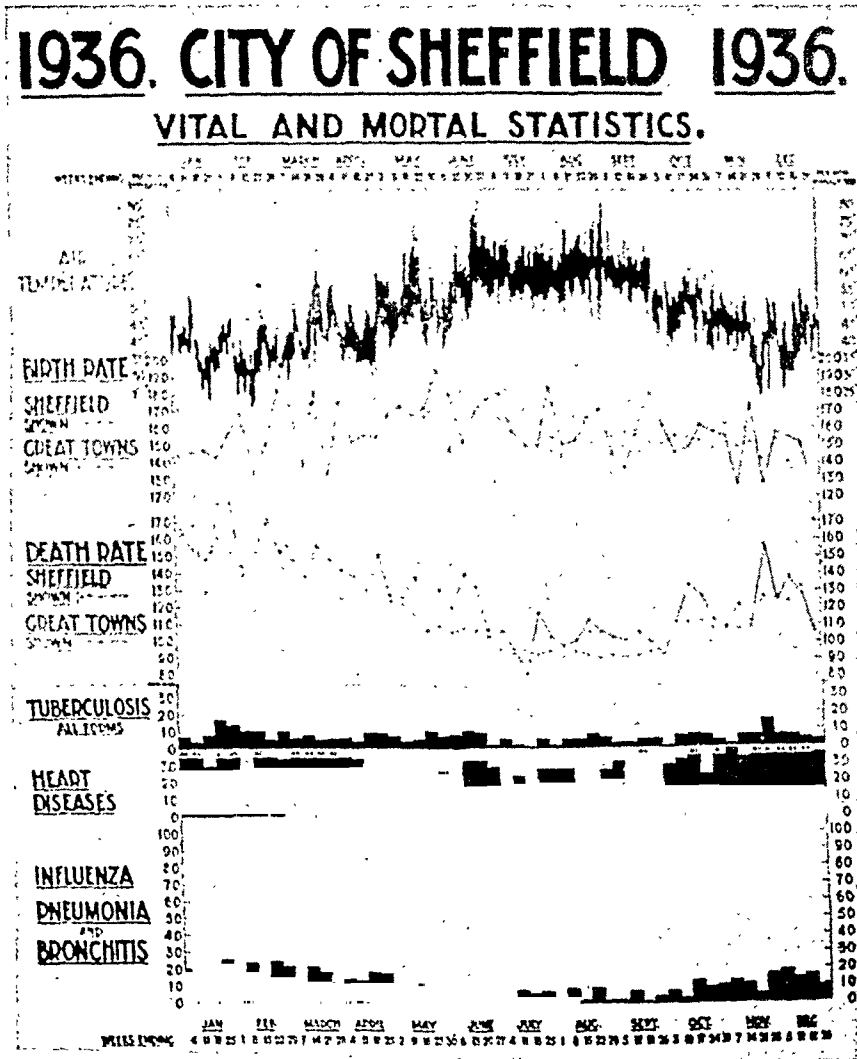


FIG. 5. The relation of mortality curves to temperature and seasons. (Annual Report on the Health of the City of Sheffield for 1936.)

sen and Mills, and show the same increase in the cold and stormy winter and spring months.

Figure 6 shows the temperature chart of five patients who were in the sanatorium at Monrovia during April and May of 1938. Their temperatures are plotted against the barometric, temperature and humidity records of the period. It will be noted that on April 22 and 23 the temperature and humidity increased, preceding a slight drop in the barometer, and that four

incidence in the fifth and sixth decades of life. The relatively mild clinical course described and mortality rate are more in accordance with reports of other authors of influenzal pneumonia prevalent at that time in large groups of over-worked and undernourished men.

REPORTED RECOVERIES FROM PRIMARY ACUTE FRIEDLÄNDER PNEUMONIA

Only 14 recoveries, including the case of the author, are available for analysis. The significant clinical data are summarized in table 3. In addition to the specific treatment mentioned, all patients received the routine supportive and symptomatic pneumonia therapy of the time.

TABLE III

Author	Year Reported	Number of Recoveries	Age	Race	Sex	Days Ill	Leuko-cytosis	Blood Culture	Treatment and Remarks
Chirié <sup>18</sup>	1906	1	17	Wh.	F.	26	?	Pos.	Colloidal silver intra-venously
Pic and Durand <sup>19</sup>	1914	1	43	Wh.	M.	22	Yes	Neg.?	Vaccine. Complicat-ing pyopneumothorax drained
Sisson <sup>1</sup>	1915	1	31	Wh.	M.	70	Yes	Neg.	Complicating pyopneu-mothorax drained. Well month after
Abrami and Worms <sup>20</sup>	1930	1	23	Wh.	M.	13	Yes	Neg.	Trypflavine intra-venously
Solomon (Bellevue Hosp.) <sup>3</sup>	1937	1	48	Wh.	M.	15	Yes	Neg.	Routine supportive treatment only
Bhatnagar and Singh <sup>12</sup>	1937	1	40	Wh.	M.	11	Yes	Neg.	Routine sup. treat. 1 :1000 agglutination titre noted
Bullowa (Haarlem Hosp.) <sup>11</sup>	1937	7	36	Neg.	M.	7	Yes	Neg.	Routine sup. treat.
			57	Neg.	M.	10	Yes	Neg.	Routine sup. treat.
			41	Neg.	M.	11	Yes	Pos.	Routine sup. treat.
			26	Neg.	M.	7	Yes	Neg.	Type A serum
			28	Neg.	M.	6	Yes	Pos.	Type A serum
			36	Neg.	M.	8	Yes	Neg.	Type A serum
Hartman	1938	1	52	Wh.	M.	12	No	Neg.	Type A serum
			70	Wh.	M.	23	Yes	Neg.	Iodides to limit of toler-ance. Sod. citrate to counteract acidosis. Digitalis, quinine and adrenalin as explained in history
Average Case Age			39						

CASE REPORT

The patient, G. V. H., was a white male, aged 70, of Hungarian extraction.

*Family History:* Not significant.

*Past History:* For the past 25 years the patient had suffered from bronchial asthma and associated chronic bronchitis. These varied in severity, usually being exacerbated in the winter. Twenty years ago he had had a septum resection and bilateral inferior turbinectomy on the advice of his physician. He had been skin tested recently with the usual allergens and found negative. By elimination, he was diagnosed as a "bacterial asthma." His sputum had been examined six times in the last five years. No acid-fast bacilli were found. A mixed flora of streptococci, pneumococci, small Gram-negative bacilli, and occasional spirillae was present. Of

tion on the fourth. Patient 10774 had been free from temperature or complications for months and developed a pleurisy with effusion which began on the fourth. Patient 10857 was a psychoneurotic who was recovering from a streptococcal infection. Note the sensitiveness to meteorologic forces as shown in the temperature elevation on the same day as the others. Patient 10817 showed a smaller elevation of temperature on the fourth than she did on the 21 and 22 of April, but it was accompanied by a mild activity in her pulmonary lesion.

In observing many patients over the past 35 years, we have noted that exacerbations of the tuberculosis and complicating lesions, such as pleurisy and hemoptysis, are atmospherically conditioned and are especially connected with storms.

Nor is the seasonal influence confined to human beings and their diseases. Brown<sup>5</sup> reports that there is an increase in the incidence and in the metastatic rate shown by mice infected with syphilis and with experimental malignancy in the late winter and early spring, and further that this harmonizes with the seasonal variation in organ size and weight.

Just what force or forces are responsible for these effects is not clear. In Southern California, where changes in barometric pressure are slight, we note the same phenomena that are noted in more rigorous climates where the fluctuations are greater. It may not be the barometric pressure or the changes in temperature which are responsible, but a combination of several or all atmospheric forces. In this connection a most interesting observation is reported by the Russian physicians who are studying man's reaction to the weather in connection with the attempt to plant colonies in the Arctic regions. They have found that two or three days before the approach of a violent Arctic winter storm the contractions of the heart decrease, sometimes to about half the normal number per minute, and that the output per contraction increases in proportion. Moreover, this occurs two or three days before any meteorologic instruments register any warning of approaching change.

Body chemistry, endocrine function and the sensitivity of the components of the vegetative system all show seasonal adaptations. In the winter the tissues are more active, cells more permeable, and the potassium is more prominent than calcium. In the summer the reverse is true. It readily can be understood that there should be a difference in the incidence of those diseases which are seasonally conditioned. It can also be surmised that there would be a difference in diseases which are conditioned by atmospheric forces.

Man is a constitutional and developmental variable, possessed of individual powers of reaction under conditions of both health and disease. He lives in an atmosphere disturbed by many forces, which are subject to diurnal, seasonal and cyclical changes. These various forces react upon his physiologic mechanism and cause many changes in its efficiency, sometimes calling out favorable response, again producing harmful effects. These

day. On the thirteenth day the temperature was only 37.6° C., and on the next day came to normal and stayed there. The pulse and respiratory rate came to normal on the twenty-third day of the illness. The chest was negative to physical examination, except for the customary faint rhonchi, by the twentieth day.

TABLE IV  
Laboratory Observations

Time	Sputum	Blood Culture	Agglutinins	Urinary Acetone Bodies	Urinary Albumin	Linzenmeier Sed. Time to 18 mm.	W.B.C.	% Neutrophiles
21 days before onset	—	—	—	0	0	145 min.	7,800	64
2nd day	Pure culture of Friedl. bac.	—	—	++	0	50 min.	12,200	82
4th day	—	Neg.	None	+	0	36 min.	15,700	85
6th day	Pure culture of Friedl. bac.	—	—	+	0	—	—	—
9th day	—	—	1:80	+++	+	20 min.	18,000	88
11th day	—	Neg.	—	+	+	—	—	—
13th day	—	—	1:320	0	+	18 min.	18,700	85
17th day	Strep. mic. catarrh. Friedl. bac.	—	1:640	0	0	26 min.	11,200	78
23rd day	—	—	—	0	0	52 min.	8,300	62

Certain features of this case are of interest. The recovery, in spite of the advanced age of the patient and the associated bronchial asthma and degenerative myocarditis, is noteworthy. Only 21 days before the onset of his illness he had been given a routine check-up, and his white blood count and sedimentation rate were known. In pneumonia due to the pneumococcus, streptococcus and Pfeiffer bacillus the Linzenmeier sedimentation rate by the second day is practically always below 30 minutes. The rapid development of specific serum agglutinins recalls the observations of Bhatnagar and Singh,<sup>12</sup> who noted the development of agglutinins to 1:1000 in their recovered case but never above 1:100 in their fatal cases. Specific serum treatment would have been attempted, but no serum was obtainable at that time in the San Francisco Bay area. Oxygen therapy was tried on the sixth day, but no benefit was noted and it was discontinued. The spectacular effect of iodide administration and its possible significance will be discussed later.

#### FACTORS AND TREATMENTS LEADING TO RECOVERY IN PRIMARY FRIEDLÄNDER PNEUMONIAS

A consideration of table 3 and a comparison of it with our knowledge of similar data in fatal cases allow the following conclusions. The average age of recovered cases is 39; this speaks for relative youth as a significant factor, as the average age of fatal cases is approximately 50. About one-half of fatal cases have a leukocytosis, the remainder having normal or subnormal counts; all except one of the recovered cases reported had a leukocytosis. Whereas only one-third of fatal cases had negative blood cultures, three quarters of the recovered cases had negative ones. Agglutinin determinations were available in only a few cases, i.e., in Bhatnagar's and some of Solomon's fatal cases (17), and in Bhatnagar's and the author's recovered cases (two). It is of in-

# CASE REPORTS

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## RECOVERY FROM ACUTE FRIEDLÄNDER PNEUMONIA; REPORT OF A CASE AND REVIEW OF LITERATURE \*

By MILTON M. HARTMAN, M.D., *San Francisco, California*

ACUTE primary Friedländer bacillus pneumonia is such an uncommon and highly fatal disease that any recovery from it should be reported in the hope that our present therapeutic armamentarium may receive some useful modification or addition. When the patient surviving this usually fatal type of infection is 70 years old at the time of his illness, thereby becoming the oldest reported case, his physician has the additional pleasure and privilege of reporting a medical curiosity.

As shown by Sisson,<sup>1</sup> Belk,<sup>2</sup> and Solomon,<sup>3</sup> primary Friedländer bacillus pneumonia presents a definite clinical picture, with a characteristic age incidence (the large majority of cases occur in the fifth and sixth decades of life), peculiar sex distribution (about six times more frequent in males), high toxicity, characteristic sputum (markedly sticky and stringy), and a high mortality. In smears of sputum the fat encapsulated Gram-negative rods, varying in length from 0.5 to 5 microns, are striking. Unmistakable are the cultural characteristics, particularly the "nail-head" appearance in gelatin stabs, and the raised, gray, sticky, mucoid colonies on agar plates. As with the pneumococcus, there are biological differences within the species. In 1926 Julianelle,<sup>4</sup> by the study of agglutination and precipitin reactions, was able to distinguish three types: A (by far the most frequent), B, and C, comprising most of the clinically important strains. All other strains fell into a heterogeneous group X. This group X will no doubt undergo the same dismemberment that the pneumococcus group IV underwent. The Friedländer bacillus, known also as the pneumobacillus, *Bacterium pneumoniae*, *Bacillus mucosus-capsulatus*, and *Klebsiella pneumoniae*, is found present in the upper respiratory tract of a small percentage of normal people. Incidences of  $\frac{1}{2}$  to 8 per cent have been reported. Bloomfield<sup>5</sup> found it in 5.8 per cent of normal people, most frequently localized in the tonsils.

The bacteriology, pathology and clinical course of primary Friedländer pneumonia have been reported in detail: we now know a good deal about the fatal cases. We do not know with any accuracy, however, the actual incidence of the disease, what clinical factors lead to recovery, and what therapy, if any, has been found effective. The author, therefore, has made as complete a search as possible of the literature from 1882 to 1937 inclusive, with particular reference to the incidence of acute primary Friedländer bacillus pneumonia as compared to that of acute pneumonias as a whole, the number of reported cases, the number of reported recoveries, and the details of treatment in the latter group. The task was complicated by the fact that when Carl Friedländer<sup>6</sup> described the dis-

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From The Department of Medicine, Stanford University Medical School. Approved for publication by Dr. A. L. Bloomfield.

ing expectorants; i.e., salts of citric acid, ammonium chloride, and hydriodic acid with its sodium and potassium salts. In this case the expectorant effect of citrates was not evident even in large doses. Ammonium chloride has the disadvantages of furthering acidosis and providing a larger nitrogen burden for the kidneys, and consequently was not even tried.

### SUMMARY

1. Approximately 5 per cent of normal people carry the Friedländer bacillus in their upper respiratory tract.
2. Acute primary Friedländer bacillus pneumonia comprises, on an average, 0.76 per cent of all acute primary pneumonias.
3. Only 284 cases of genuine Friedländer bacillus pneumonia have been mentioned in the medical literature from 1882 to 1938.
4. In only 233 cases are satisfactory clinical records or summaries available.
5. Of these 233 cases, 219 were fatal. The mortality rate is 94 per cent.
6. Only 13 recoveries have been reported previous to the author's case.
7. The author's patient contracted his illness at the age of 70 and is the oldest known patient to have recovered.
8. Significant clinical data on the 14 recoveries are summarized.
9. The author's case is reported in detail, with complete laboratory investigation.
10. Only surgery for complications and serum have thus far been helpful as additions to routine supportive therapy.
11. The use of iodides in the author's case and its rationale are reported.

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small series of pneumonias, whereas others have reported an extremely low incidence. Interesting extremes are those of Bhatnagar and Singh,<sup>12</sup> who found 13 cases in 100 consecutive pneumonias in India, and of Baehr, Schwartzmann and Greenspan,<sup>13</sup> who found only two cases in the last 36 years at the Mount Sinai Hospital, New York (a hospital of 856 beds having 14,749 admissions in 1936).

#### REPORTED CASES

In 1915 Sisson<sup>1</sup> completely reviewed the literature on primary Friedländer bacillus pneumonia to that date. Because of the previously mentioned unsettled status of bacteriological technic and classification and the early pneumobacillus-pneumococcus controversy, he was forced to conclude that up to that time only 33 cases had been so fully studied and reported that they could be considered pneumonias due primarily and solely to the Friedländer bacillus. These included only two recorded recoveries, a case of Chirie in 1906 and one of Pic and Durand in 1914. He mentioned that Apelt and Phillippi each had had one recovery, but neither of these cases was mentioned or reported in journals by the authors themselves; their reported cases were all fatalities. Sisson also mentioned Stuhlern's three recoveries in a series of 10 cases in 1904, but he strongly doubted (as does the author) that Stuhlern was dealing with the Friedländer bacillus. Sisson reported four cases of his own, including one recovery. The situation, then, in 1915, was 37 recorded cases with three recorded recoveries.

The author was able to discover in the more voluminous and more accurate literature since Sisson's day an additional 247 cases, in both case reports and in mere mention in various pneumonia series. In 196 cases (80 per cent) complete clinical records or satisfactory summaries were obtained, either in journals or personal communications from hospital staffs and living authors. The 51 remaining cases were reported from reliable institutions but no further information was obtainable except that they had occurred. The mortality in this latter group is pure speculation; presumably all cases died.

#### RECORDED FATALITIES AND RECOVERIES FROM FRIEDLÄNDER PNEUMONIA

TABLE II

Sisson 1882-1915	34 fatalities	3 recoveries
Hartman 1915-1937	185 fatalities	11 recoveries
Totals	219 fatalities	14 recoveries
	Fatalities plus recoveries 233	
	Mortality 94 per cent	

It was interesting to find that only five cases had been reported in children: Etienne<sup>14</sup> reported one in 1895, Comba<sup>15</sup> one in 1896, Ferguson and Tower<sup>16</sup> two in 1933, and C. H. Smith at the Bellevue Hospital, New York, one in 1937. In 1916 Zander<sup>17</sup> described an epidemic of what he thought was acute primary Friedländer bacillus pneumonia in a German labor camp. His report of 144 recoveries in a group of 411 cases was amazing. However, he performed no autopsies, and made no sputum smears or cultures and no serum agglutination tests, his diagnosis being made entirely on clinical evidence. His average age of 25 years and mortality rate of 35 per cent are entirely at variance with the experience of other investigators who have noted the high mortality and peak



had no asthma during the winter. Direct skin testing with Squibb's Catarrhal Vaccine No. 5, and with the *Staphylococcus aureus* and *Staphylococcus albus* therein (E. R. Squibb Co. kindly supplied me with the individual components of their mixed respiratory vaccine) have remained strongly immediately reactive, but passive transfer has failed. The patient has since developed spring hay-fever due to grasses, and both the direct and indirect reactions are present to this atopen.

### SUMMARY

A case of respiratory allergy is reported in which repeated immediate constitutional reactions of the explosive type occurred following the subcutaneous injection of a stock vaccine. Repeated efforts passively to transfer the reaction of the vaccine to the skin of a substitute failed. Mention is made of this effort to transfer the reaction by the Prausnitz-Kustner technic because of the moot question of the transferability of bacterial reactions.

### CONCLUSION

That the explosive type of constitutional reaction following the injection of bacterial vaccines is rare, but does occur, is the conclusion drawn.

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## MYCOTIC ANEURYSM; REPORT OF ONE CASE\*

By VINCENT WILLIAM KOCH, M.D., F.A.C.P., and  
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*Janesville, Wisconsin*

### CASE REPORT

R. C., a white male, 43 years of age, was seen on December 10, 1935, complaining that for two days he had been having severe head pain in the right frontal area. He had been ailing since August 1935, when he had developed cerebro-spinal meningitis. At that time he had been treated by spinal drainage and instillation of four doses of serum. He had recovered in four weeks, but had continued to feel very weak. About October 1 he began to feel pain in his joints, particularly in the knees and hips, and running down into his feet. His feet felt stiff when he arose in the morning, but after moving about they would gradually loosen up. Pain developed in the right kidney area and radiated to the right groin. He ran an elevated temperature, with chills. He complained of urinary frequency, and the urine contained pus. A cystoscopic examination showed only a kinked ureter, and following the examination the complaints of frequency and kidney pain ceased. A few days before the visit of December 10 he had a tooth extracted because of pain in the right upper jaw and in the right side of the head. There was not much bleeding at the site of the extracted tooth. On December 8 he developed headache which was located over the right eye and right frontal area. The pain became very severe, and, as the severity increased, he noticed difficulty in the use of his left upper extremity. The morning of Decem-

\* Received for publication March 21, 1940.

note in light of later events is the fact that the administration of iodides to the limit of tolerance never made any difference in the character of his sputum, the ease of expectoration or the severity of the asthma. A roentgen-ray of the chest two years ago showed bronchial markings increased, mainly in the lower lobes, and no suspicion of tuberculous lesions. Twice in the past three years the patient had had symptoms of dyspnea on exertion and had responded well to a therapeutic test of digitalization.

*Present Illness:* On November 28 the patient felt a sense of oppression in the chest and noted that his asthma was not as well controlled by his prescription of ephedrine and phenobarbital as usual. His sputum, usually raised without difficulty, became brownish, "very sticky," and "hard to bring up." On November 29 he felt feverish and very dyspneic. Examination then showed a very dyspneic man of 70, not cyanotic, T. 38° C., P. 76, R. 32, and B.P. 126/62. His chest was of the emphysematous type and filled with sonorous and sibilant rhonchi throughout. There were a moderate number of moist râles at the bases. Present also were dullness and transmission of whispered voice sounds over the upper division of the right lower lobe. The liver was palpable two fingers'-breadth below the right costal margin. The sputum was a homogenous brick-red, very thick, and peculiarly sticky and stringy. The Gram stain showed great numbers of large Gram-negative encapsulated rods and a very rare Gram-positive coccus. A pure culture of Friedländer bacillus of Julianelle's Type A was recovered. The only urinary abnormality was a two-plus acetone. The sedimentation rate by Linzenmeier's method was 18 mm. in 50 minutes. There were 12,200 white blood cells, with 82 per cent neutrophiles.

*Progress and Treatment:* Epinephrine 1:1000 hypodermically was administered frequently. In asthma-free intervals the classical signs of consolidation were obtained over the upper portion of the right lower lobe. Small doses of quinine controlled the chills that the patient started to have. Dyspnea unrelieved by adrenalin, an increase in basal râles, a lowering pulse pressure (B.P. 100/54), and an occasional extrasystole on the second day suggested a weakening myocardium. Digitalization was rapidly effected and maintained throughout the illness, with benefit to the dyspnea, reduction of the râles, and maintenance of the blood pressure up to an average of 130/64 for the remainder of the illness. The height of the fever was reached on the fifth day and was maintained until the twelfth day. The temperature swung from 36.4° C. to 39° C. daily; the respirations varied from 26 to 38 (depending on the amount of adrenalin effective at the time), and the pulse remained at 94 to 100. The right lower lobe became completely consolidated by the fifth day, and a suspicious patch had appeared in the left lower lobe posteriorly.

From the very beginning sodium citrate had been given for the dual purpose of counteracting acidosis and liquefying the sputum. Although the ketonuria was kept to a minimum and the urine usually alkaline to methyl-red indicator, the expectorant effect was nil; the consistency of the sputum remained unchanged. On the fifth day, therefore, it was decided to try the effect of stopping sodium citrate and using sodium iodide to the limit of tolerance as judged by rhinorrhea. The effect was remarkable: the sputum became much thinner and was brought up with ease; adrenalin became necessary only infrequently; the subjective condition of the patient improved immediately; and the signs disappeared from the left lower lobe. By the eighth day, however, a mild acidosis was evident clinically and the ketonuria was marked. Sodium citrate was substituted for the sodium iodide; the acidosis was checked but the sputum became thick and sticky again. Adrenalin became necessary frequently, and the patient felt much worse. Examination on the tenth day showed the right lower lobe consolidated, and slight dullness with moderate diminution of breath sounds over the left lower lobe. The left diaphragm was apparently elevated also. Sodium citrate and sodium iodide were then administered together, with the same spectacular effect previously noted. The signs over the left lower lobe were gone by the next

slightly increased pressure. On the basis of the history and initial findings it was felt that the diagnosis lay among the following: (1) subarachnoid hemorrhage from a small vessel; (2) cerebral abscess as a sequel to cerebrospinal meningitis; (3) bacterial endocarditis with ruptured mycotic aneurysm.

The patient was put to bed at once on December 10, 1935, and morphine sulphate, gr.  $\frac{1}{4}$ , was given p.r.n. for pain. Since this was believed to be a case of subarachnoid hemorrhage, a second spinal puncture was done the same day. The fluid was bloody, and contained 153 white blood cells per cu. mm., with the lymphocytes predominating. For therapy two spinal punctures were ordered daily, and fluids were forced by mouth



FIG. 2. Necrosis of artery wall at site of rupture, with embolus containing bacteria attached to intima.

and hypodermoclysis. Because the spinal fluid was very bloody, the temperature not elevated, and the white blood cell count only 9,200, the diagnosis of cerebral abscess was discarded. A roentgen-ray of the skull gave no evidence of tumor or other pathologic condition. The motor paralysis of the left side became more extensive and began to exhibit spasticity. During the course of the first week the patient became completely paralyzed on the left and at the same time very irrational. The temperature began to rise on the fourth day, and the elevation continued intermittently. The spinal fluid cleared on the sixteenth tap. A culture of the fluid gave no growth. A blood culture on December 18 gave a positive growth and the smear showed streptococci. The following three blood cultures were positive, and therefore a definite

terest to note that in none of the fatal cases did the agglutinins, if present at all, go above 1:100, but that in the two recoveries the agglutinins reached 1:640 and 1:1000. The administration of intravenous colloidal silver and of tryptoflavine have been shown to be useless gestures in other types of bacterial infection, and the two cases mentioned probably recovered in spite of these measures rather than because of them. The disease is too fulminating to permit of vaccine therapy, the patients already producing their own vaccine. Routine supportive and symptomatic therapy (including oxygen), so important in all pneumonias, has been supplemented so far only by surgery, specific serum, and iodides. In reviewing the fatalities one is struck by the number of cases complicated by empyema and pulmonary abscess undiagnosed during life. Appropriate drainage by surgical means would probably have saved some of these lives. The claim might be made that these patients are too sick to stand diagnostic and therapeutic procedures, particularly surgical ones, but our present 94 per cent mortality by conservatism indicates that we probably have much more to gain than to lose by apparent radicalism.

Serum treatment of Friedländer pneumonia is in its experimental stage. Theoretically it is the ideal treatment. Practically, there are difficulties in the way of its universal application. The serum is available only in a few eastern centers. Diagnoses of Friedländer pneumonia (during life) are so infrequent that no one investigator can make a critical evaluation of serum treatment from personal experience, and the likelihood of deterioration of the serum to nil potency between cases is a real one. Neither public nor private institutions like to assume the expense of having on hand at all times fresh stocks of a serum for which they have infrequent calls. Like all therapeutic sera, it should be given early to be most effective; airplane service, if used, would help realize this aim. Judging from our past experiences with sera for even the common diseases, the cost will be prohibitive for some time to come. Three recoveries in six of Bullowa's (Haarlem Hospital) cases in which the serum was given early enough to be effective may be only coincidence, but the report certainly is encouraging.

To make any generalizations on the usefulness of iodides on the basis of one case is unscientific. The effect, however, was interesting. Its use in the reported case was prompted by a study of the pathology of Friedländer pneumonia. In pneumococcal, streptococcal and influenzal pneumonias we have to deal with a parenchymatous process practically from the onset. The stages of engorgement, red hepatization, gray hepatization, and resolution affect each area usually in uncomplicated sequence; atelectasis and bronchial inflammation are minor features. With Friedländer bacillus pneumonias, in addition to this classical picture, there is a significant bronchial and bronchiolar involvement. The peculiarly sticky, stringy exudate which we later see as sputum blocks the smaller and often the larger air passages. The resulting areas of atelectasis undergo secondarily both the classical pneumonic and the necrotizing types of inflammation. Although useless in other types of pneumonia, a liquefying expectorant can evidently be of value in the Friedländer type. The patient should be enabled to dispose of his bronchial exudate with ease, with a resulting prevention of atelectases and a conservation of effort. The reported case is the first in which liquefying expectorant therapy in primary Friedländer bacillus pneumonia was tried. In actual practice we are limited to three types of liquefy-

bolism with thrombosis and encephalomalacia; necrosis of wall of the cerebral artery with rupture, hemorrhage and cyst formation; multiple infarcts of the spleen with degeneration and liquefaction; bilateral infarcts, both recent and old, of the kidneys; multiple petechial hemorrhages of the mucous membranes and skin; marked emaciation.

The body was markedly cachectic, with scattered petechiae and ecchymoses in the skin over the abdomen and chest, the hemorrhages measuring from pin-point size to 3 mm. in diameter. The conjunctivae were studded with petechiae.

The lungs were partially collapsed. Both pleural cavities were free of fluid. The superior lobe of the right lung was crepitant throughout, while the middle and

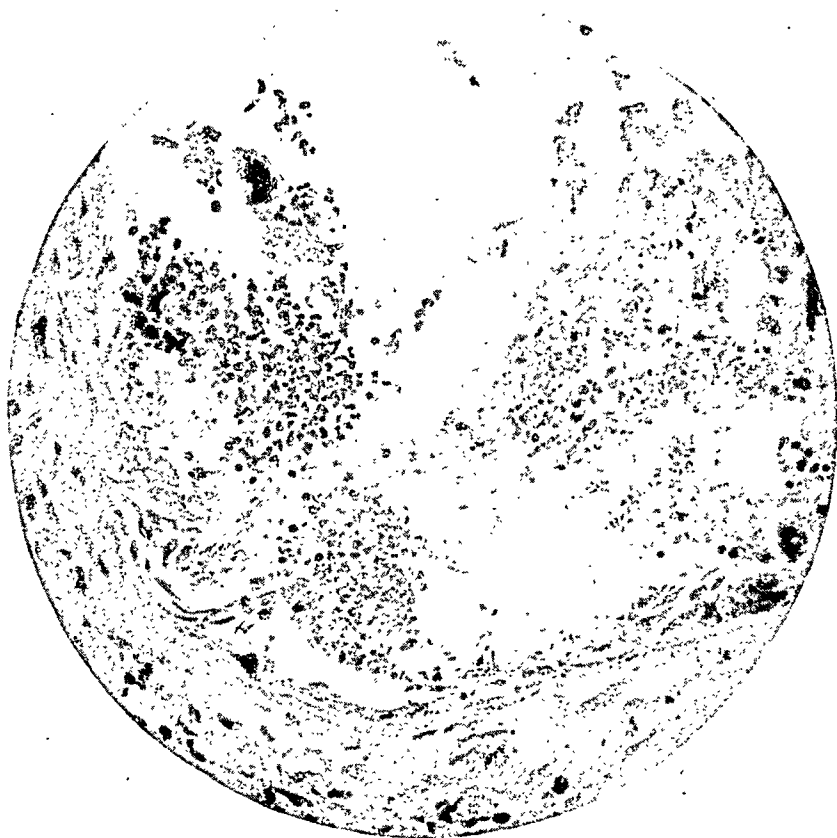


FIG. 4. Infected embolus of artery wall partially recanalized.

lower lobes were discolored, mottled, bluish-red, heavy and firm. The cut surface was very wet, dripping frothy exudate, and was grayish-red in color, having the appearance in portions of gray hepatization. The left lung was similar to the right.

The pericardial sac was greatly distended and contained about six ounces of clear, straw-colored pericardial fluid. The heart was in systole. The visceral pericardium was somewhat thickened with gray patches. The heart weighed 340 grams. The mitral valve ring measured 10 cm. in circumference. The anterior leaflet was covered by a thick, verrucose vegetative growth that covered the distal half of the leaflet, and extended upward over the lateral left auricular wall over an area measuring 5.5 cm. in diameter. This vegetative growth extended downward onto the chordae

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## CONSTITUTIONAL REACTIONS FROM BACTERIAL VACCINES \*

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THE recent communication of Brown<sup>1</sup> indicates that constitutional reactions from bacterial vaccines *never* resemble those occurring from injections of protein extracts. Herewith is reported an exception, the only one I have observed in 240 asthmatics treated with bacterial vaccines.

### CASE REPORT

E. J. D., male, aged 12, with a history of winter asthma of bacterial origin since the age of three, and under my care since the age of six, in the fall of 1937 gave a very strong immediate whealing reaction from the intradermal injection of 0.02 c.c. of Squibb's Catarrhal Vaccine No. 5. A moderately strong direct reaction to house dust was also present. All other direct tests with foods and inhalants were negative. Passive transfer was negative for all excitants, including both the dust and the vaccine.

Pre-winter treatment, with weekly alternating doses of dust and vaccine was begun, each dose being increased by 0.05 c.c. Two minutes after the subcutaneous injection of the 0.35 c.c. dose of the vaccine (with suction precaution) a severe explosive constitutional reaction of the protein extract type occurred; the symptoms developed were itching and swelling of the conjunctivae, itching of the nose and throat, sneezing, dyspnea, suffocating cough and urticaria. One week later, the dose of 0.35 c.c. of the vaccine was repeated, and the immediate constitutional reaction, though not so severe, again occurred. Treatment was discontinued and the patient

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## DISCUSSION

Descriptions of mycotic aneurysms are uncommon in medical literature, and clinical diagnosis of their presence prior to autopsy is very rarely made. Such aneurysms develop in the course of a bacteremia, which may be of any origin, but most commonly that associated with bacterial endocarditis. The infecting organism may be any one of many varieties. The affection occurs during the earlier years of life rather than in middle life and old age. The heart, aorta, medium-sized and small arteries may be involved, and involvement of veins<sup>1</sup> has been described as well. According to Reifenstein,<sup>2</sup> the first description of an embolomycotic aneurysm was apparently made by Koch in 1851, his case being that of a ruptured mycotic aneurysm complicating an acute endocarditis. Ponfick, Pel, Osler and others have since reported additional cases and have described the method of formation of the aneurysm. In the smaller vessels the condition is due to the direct lodgement of infected emboli, often at the bifurcation of the small arteries. Infection and erosion of the artery wall follows, and an aneurysm is produced by pressure on the weakened vessel. Osler<sup>3</sup> states that the process is favored in vessels which receive little support from surrounding tissues; hence, the frequent occurrence of such aneurysms in the mesenteric, cerebral and the more superficial peripheral arteries. The process differs in the case of the multiple mycotic aneurysms of the aorta, which in all probability usually arise from emboli in the vasa vasorum. Symptoms are likely to arise during the stage of inflammation of the vessel wall, if the vessel be superficial, consisting of pain and swelling at the site. On the other hand, in an organ such as the brain, symptoms arise in the event of rupture of the aneurysm. In many cases no symptoms are noted, and the condition is recognized only at autopsy or not at all.

The present case was one in which a diagnosis on the basis of clinical and laboratory findings was possible before death. A man of 43 presented the picture of sudden onset of hemiplegia restricted to the right cerebral hemisphere, increased intracranial pressure, and prolonged hemorrhage into the subarachnoid space. On the other side of the picture was the gradual increase in weakness and weight loss, the chills and fever, a mitral murmur, the embolic phenomena, and a positive blood culture completing the story of subacute bacterial endocarditis. Considered with the rest of the history, these circumstances justified the diagnosis of ruptured mycotic aneurysm of a cerebral artery, which was verified at autopsy. The remainder of the autopsy picture was that commonly seen in cases of subacute bacterial endocarditis.

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ber 10 his pain was so severe that he could not sleep and had one vomiting spell. Review of history by systems revealed further that for the past month he had had frequent chills and felt cold most of the time; his appetite was poor, and the bowels were constipated; his strength had been gradually failing; and his weight had dropped from 160 to 140 pounds.

The past medical history included the usual childhood diseases. He had had bronchopneumonia while in France during the war, and scarlet fever in 1918 at Camp Grant. Cerebrospinal meningitis in August 1935 had left some deafness of the left ear. A herniotomy had been performed 10 years previously, and a finger had been amputated during boyhood due to a corn-shredder accident.

The family history revealed that the mother had suffered a cerebral hemorrhage, and one brother had died with tuberculosis. The social history contained nothing of interest.

On examination the patient appeared as a tall, slender, anemic male who walked with a tendency to fall to the left. He was fairly well nourished, and mentality was



FIG. 1. Recanalized, partially hyalinized thrombus with necrosis of wall and rupture of cerebral artery.

fair, except that he appeared drowsy. The temperature was 98.6° F., pulse 64, and respirations 16. There was tenderness and relative dullness over the right frontoparietal area, and orbital tenderness was present on this side. The pupils were equal and reacted to light and accommodation. The left ear was partially deaf. The nose and the eyegrounds were normal. The left side of the mouth was somewhat dropped. The teeth bore fillings, and some were missing. The tonsils were absent.

A slight rigidity of the neck was observed and the head could not be flexed upon the chest. The submaxillary nodes were palpable, but the glandular system was otherwise negative. The pulse was slow, and the blood pressure was 106 mm. Hg systolic and 90 mm. Hg diastolic. The chest was long and thin, and the lungs clear. There was left-sided cardiac enlargement, and a mitral systolic murmur. The abdomen was not abnormal except for a herniotomy scar on the left. The skin was normal. The findings in the neuromuscular system were outstanding: There was hemianesthesia of the entire left side, and partial motor paralysis of the left upper and lower extremities. The left side of the face was dropped slightly, and on this side the patient was able to show his teeth less well than on the right. Reflexes were relatively increased on the left, and Babinski's and Gordon's signs were present. A positive Kernig's test was elicited. The spinal fluid on lumbar puncture was bloody and under



normal. These additional findings on the blood chemistry were normal: alkaline reserve 51 per cent, chlorides 575 mg., total protein 7.11 mg., serum albumin 4.43 gm., serum globulin 2.68 gm. The average readings for the blood calcium were 7.5 mg. and for phosphorus 7 mg. With the onset of menstruation the calcium dropped to 6 mg., the phosphorus rose to 9 mg. and tetany would appear. In another day or two the calcium was reduced below 6 mg. and convulsions occurred. The blood calcium remained at a low level for a week after menstruation and at this period also convulsions occurred. The administration of parathormone during the menstrual period prevented this marked drop in calcium. For example, on one occasion when 20 units of parathormone were given daily for two days premenstrually the blood calcium was 9.5 mg. and the phosphorus was 5.6 mg. at the onset of menstruation. With the continued daily injection of parathormone the blood calcium was 8.2 mg. and the phosphorus 7.3 mg. at the end of a five-day menstrual period. The menstrual periods were irregular, often 10 to 14 days over the usual 28 day cycle. The flow was scant although it lasted for five days. A study of the calcium metabolism<sup>1</sup> revealed retention of calcium in her body, amounting to 0.98 gm. of calcium per day. When the experiment was repeated and 20 units of parathormone were administered daily there was an increased excretion of calcium. The increased excretion was mainly in the urine, bearing out the experience of Albright, Bauer, Ropes and Aub.<sup>2</sup>

Attempts to keep the blood calcium elevated by means of various calcium preparations in large doses by mouth met with failure. A low phosphorus diet plus large amounts of calcium by mouth was unsuccessful. Ammonium chloride in large doses was of no avail. Viosterol up to 3 c.c. daily did not help. Parathormone had to be used to keep the patient out of difficulty. It was usually given about two days before the expected period, during the menstrual period and for a few days after. From February 1933 the parathormone was used regularly at each menstrual period. The initial dose was 20 units daily but it was soon found, in accordance with the experience of others, that the dose of parathormone subcutaneously had to be increased. Within a year even up to 100 units twice a day did not keep the patient from tetany and convulsions.

In March 1934 the patient went to Johns Hopkins Hospital where Dr. Owings did a parathyroid graft by his special technic. This was unsuccessful and in May 1934 the procedure was repeated. The patient improved and did not require parathormone for almost one year. In April 1935, however, her difficulty recurred and she was admitted to the Long Island College Hospital in July 1935. At that time the patient had a definite psychoneurosis. She would not get out of bed because of the fear of a convulsion. She was placed on a low phosphorus diet with calcium gluconate by mouth. Parathormone was again administered at the menstrual period, the average dose being 50 to 100 units daily. For the next two years the patient did fairly well. She was disturbed by mild carpopedal spasm at the time of her menstrual period. An increase in the dose of parathormone apparently was not needed.

In June 1937 the patient married. She became pregnant shortly afterward and did very well during her pregnancy. The blood calcium in the fifth month of her pregnancy was 8.8 mg. She was able to carry on full physical activities for the first time in nine years. She was delivered of a normal infant on March 22, 1938. Two days afterward the blood calcium was 8 mg. and the phosphorus 6.1 mg. A week later the calcium was 6.6 mg. and the phosphorus 7.3 mg. The patient did not nurse the baby and about one month after delivery the menstrual period returned with the attending tetany and convulsions.

Her recurring difficulty at each menstrual period necessitated readmission to the hospital on November 22, 1938. The patient showed the usual signs of tetany and she was very apprehensive. A slit-lamp examination by Dr. Robert M. Rogers showed beginning cataract formation. The blood calcium was 6.5 mg. and the phos-

diagnosis of subacute bacterial endocarditis with ruptured mycotic aneurysm was made. Blood transfusions were tried to combat the progressive infection and anemia. Intravenous medication with sodium cacodylate in five grain doses was started on December 25, 1935, and 10 injections were given.

The progress of the patient was steadily downward. The delirium, fever and pulse rate increased. Petechiae appeared on many parts of the body. Joint redness and swelling occurred, and motion in the affected joints was very painful. The fluid intake and output were fairly constant, although the urine contained blood. The spleen and liver became palpable and very tender. The white blood cell count rose

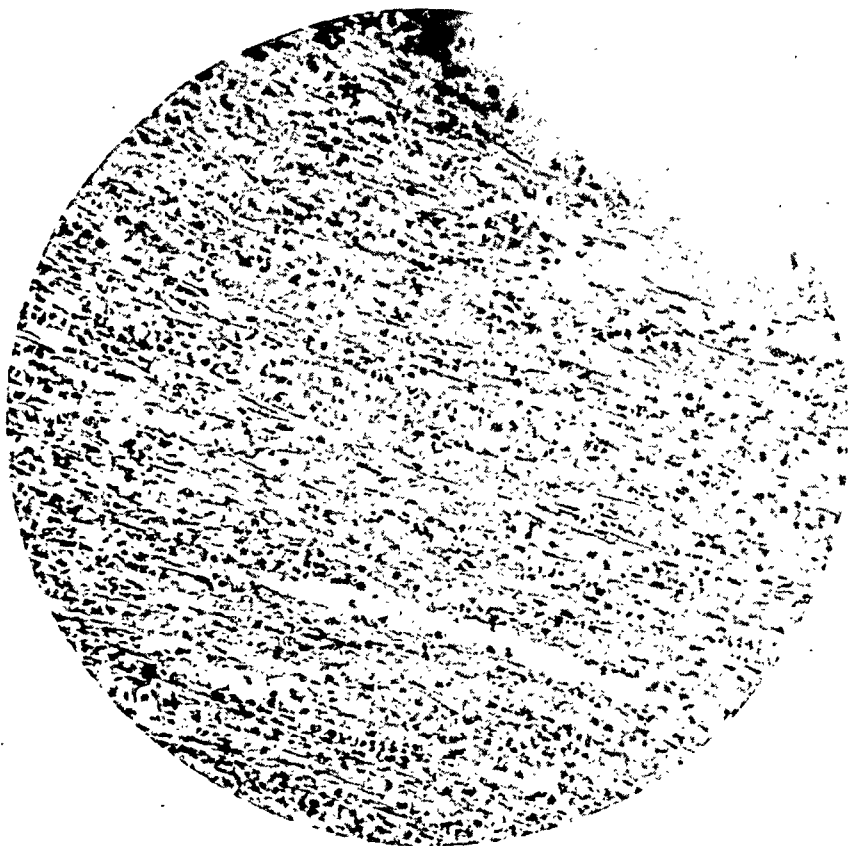


FIG. 3. Dense polymorphonuclear cell infiltration of artery wall adjacent to site of rupture.

on December 20 to 19,000 with 83 per cent neutrophils, but fell to 7,000 on January 6, 1936, with 82 per cent neutrophils. After a long period of increasing helplessness, mental confusion, and cardiac weakness the patient died on March 6, 1936. The final clinical diagnosis was: (1) subacute bacterial endocarditis; (2) ruptured mycotic aneurysm of artery in right cerebral hemisphere.

#### AUTOPSY REPORT

*Anatomical Diagnosis:* Acute vegetative endocarditis of mitral valve; pericarditis with effusion; bilateral confluent bronchopneumonia; multiple cerebral artery em-

but it acts more slowly and over a longer period of time. The first increase in blood calcium is noted in about 48 hours, and with small doses a normal blood calcium is reached in seven to 14 days. The blood phosphorus shows a slight initial rise, then falls as the calcium approaches normal. The effect on the calcium persists for one to three weeks after discontinuation of the drug. Only small amounts of the drug are necessary after a normal blood calcium is reached and frequent determinations of the blood calcium must be made before the maintenance dose is established. Mac Bryde<sup>8</sup> recently reported the successful treatment of seven cases of parathyroid tetany with dihydrotachysterol. These patients have been kept free of symptoms for some period of time.

Overdosage with dihydrotachysterol causes the same toxic effects as overdosage with parathyroid extract and these are attributable to hypercalcemia. The early symptoms are anorexia, nausea, vomiting; these are followed by headache, thirst, stupor, ataxia, and exanthems. The drug should be stopped, the patient should be at complete bed rest and large amounts of fluid administered both by mouth and parenterally.

### CONCLUSION

A case of chronic idiopathic parathyroid insufficiency of 10 years' duration complicated by convulsions at the time of menstruation has been remarkably improved by the use of dihydrotachysterol. All types of calcium therapy and diets, parathyroid extract and parathyroid gland grafts, though of some temporary benefit, were ultimately inadequate. This case bears out the experience of others in that dihydrotachysterol is very successful in the treatment of parathyroid insufficiency.

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tendineae and anterior papillary muscle. The growth had confined itself mainly to the anterior leaflet. There was no evidence of calcification. The left ventricular wall measured 1.5 cm. in thickness in the middle third. The aortic ring measured 7.5 cm. in circumference. The aortic valve leaflets were grossly normal, and the endocardium was smooth and normal, down to the mitral ring. The pulmonic valve measured 7 cm. in circumference, and the valve leaflets were grossly normal.

There was no free fluid in the peritoneal cavity. The omentum was almost entirely devoid of fat. The intestines, including the stomach and large bowel, were collapsed and grossly normal. The gall-bladder was distended with bile and the bile ducts were patent. The spleen was adherent to the stomach, was surrounded by the omentum, and was also adherent to the peritoneum by dense, fibrinous adhesions. It was very much enlarged and weighed 365 grams. On the lower pole there were two large, discolored areas measuring 2 and 1.5 cm. in diameter. The capsule was tense, and the entire organ felt soft. The cut surface revealed the two areas in the lower pole to be large infarcts, measuring 2 by 3 and 1.5 by 2 cm., gray-red and firm. In the center there was a large infarct measuring 5 cm. in diameter, which had undergone degeneration and liquefaction. There were numerous smaller infarcts scattered through the parenchyma. The liver weighed 1400 grams, and was normal in all respects. The right kidney weighed 125 grams and the left weighed 140 grams. The surface was studded with grayish and hemorrhagic areas, varying from 6 to 8 mm. in diameter. The cut surfaces revealed the cortex and medulla studded with numerous infarcts, some of which had undergone fibrosis and others of which were hemorrhagic. The capsule stripped with some difficulty, especially overlying the infarcts. The lining of the pelvis was studded with petechial hemorrhages. The left kidney was similar.

**Brain:** There was old blood pigment staining over the membranes covering the right occipital and parietal lobes and over the inferior surface of the left temporal lobe. A blood clot was present about the vessels in the left Sylvian fissure. There was a thrombus at the bifurcation of the left middle and posterior cerebral arteries beyond which point there was an area of encephalomalacia involving the tissue adjacent to the Sylvian fissure. On multiple transverse section of the brain it was revealed that the encephalomalacia involving the tissue adjacent to the left Sylvian fissure was rather superficial, but adjacent to the base on the left it extended more deeply into the underlying tissue. In this area are multiple small thrombosed vessels. Anteriorly on the right and immediately lateral to the thalamic tract was a thrombosed vessel with rupture and extravasation of blood cells into the surrounding tissue for an area 3 cm. in diameter. In the gray matter of the right temporal lobe was situated a cavity approximately 2 cm. in diameter filled with old blood, soft in consistency and lined by yellowish membrane, tapering to an area pointed in shape anteriorly and posteriorly with softened brain tissue surrounding and extending to a distance of about 6.5 cm. The area of hemorrhage lay immediately beneath the lateral surface of the right lateral ventricle. The lining of the right lateral ventricle showed congested vessels. Section of the pons and medulla showed no gross changes.

**Microscopic Diagnosis.** Section of the brain showed an area of necrosis and old hemorrhage with a border of phagocytes containing iron pigment, occasional polymorphonuclear and round cells. In the same section was a large artery with hyalinized areas of intima, a hyalinized and recanalized thrombus and an infected embolus consisting of bacteria plus polymorphonuclear and round cells.

Section of kidney showed multiple emboli of the glomeruli.

The lung exhibited bronchopneumonia and edema.

The liver showed chronic passive congestion and miliary abscesses.

The spleen exhibited infarcts with central abscess formation, and chronic passive congestion.

equivalent to 40 per cent of the serum protein eaten. Fairly effective were kidney, liver, casein, muscle, bran, and rice; heart, brain, spleen, stomach, and red blood cells were poor. The incomplete proteins, gelatin and zein, were inert.

The addition of certain amino acids to the diet also increased plasma protein formation—perhaps because they supplemented some relatively incomplete proteins in the diet. Cystine, leucine and glutamic acid were the most efficient and apparently the most important in this respect.<sup>3</sup> The rest of the nine or ten amino acids found necessary for growth in rats by Rose are probably also required, but direct proof of this is still lacking.

The site of synthesis of the plasma protein is still disputed. There is strong evidence that fibrinogen and prothrombin are formed only in the liver. Whipple believes that the albumin and much of the globulin are also found in the liver. This is based largely on the low plasma proteins formed after partial hepatectomy or experimental liver injury, and clinically in cirrhosis and allied conditions associated with liver injury. On the other hand antibodies—and possibly other globulins—are undoubtedly formed by the cells of the reticuloendothelial system generally.

The most interesting point brought out by these studies is that the plasma proteins constitute functionally an integral part of the general body proteins and are not isolated and independent substances. In a starving animal, homologous plasma protein injected intravenously will not only elevate the blood protein of the recipient but will maintain the animal in nitrogen equilibrium. Manifestly this protein has been seized by the body cells and utilized in their metabolism, and this is accomplished without any loss of nitrogen, as determined by a study of urinary excretion. On the other hand, if an animal which is fasting is bled so as to reduce the plasma protein sharply, there will be a substantial rise in plasma protein within a few hours, which may continue at a less accelerated pace for some days. This increment manifestly must come from protein or protein building materials from the tissues. This reserve store of protein is also shown by Whipple's experiments on standard depleted dogs, in that the amount of bleeding required to maintain hypoproteinemia is substantially greater during the first few weeks than in the later stages of the experiment. This excess protein so removed is a measure of the reserve stores of the body and may amount to from 100 to 200 per cent of the normal circulating plasma protein. The reserve store may also be depleted by protein starvation. It may be regarded as analogous to the body stores of carbohydrate (glycogen) and fat. Serious depletion of the stores results in lowered resistance to infection and to certain intoxications.

The exact nature and location of these protein stores is not definitely known. It can not be recognized histologically, like glycogen or fat. No

<sup>3</sup> MADDEN, S. C., FINCH, C. A., SWALBACH, W. G., and WHIPPLE, G. H.: Blood plasma protein production and utilization. The influence of amino acids and sterile abscesses, Jr. *Exper. Med.*, 1940, lxxi, 283-297.

PARATHYROID TETANY: CHRONIC IDIOPATHIC PARATHYROID INSUFFICIENCY OF TEN YEARS' DURATION  
SUCCESSFULLY CONTROLLED WITH  
DIHYDROTACHYSTEROL\*

By SAVERIO C. FRANCO, M.D., *Brooklyn, New York*

CASE REPORT

The patient was a young woman, 23 years of age, who was admitted to the Long Island College Hospital for the first time in April 1932. At that time she was 17 years of age and her presenting complaint was convulsions.

The family history was irrelevant. Her past history revealed scarlet fever at four years, right mastoidectomy at seven years, measles and chickenpox at 10 years.

Her present illness began with the onset of her menstrual cycle at 14 years of age in the summer of 1929. Forty-eight hours after the onset of her first period she developed tetany with carpopedal spasm. When this recurred for several menstrual periods she entered Bellevue Hospital where she was successfully treated with calcium and viosterol. The patient remained well until November 1930 when the tetany returned at the time of her menstrual period. On this occasion she had her first convulsive seizure. She stated that a certain word kept repeating itself in her mind and then she lost consciousness. According to the description given by her family there was a carpopedal spasm followed by clonic shaking movements of her arms and legs lasting one-half to one minute. After the convulsion she was drowsy for an hour. It was noted that she had bitten her tongue. These convulsions recurred at her next three menstrual periods. In February 1931 she had convulsions several times a day and night during her menstrual period. She was admitted to Bellevue Hospital where a diagnosis of epilepsy was made. The patient was placed on bromides, a high fat diet, and restricted water intake. After two months' treatment she was so improved that she was free of any convulsions until January 1932. Then, the convulsions recurred at the time of the menstrual periods and in April 1932 she was admitted to the Medical Service of the Long Island College Hospital on the service of Dr. E. R. Marzullo. The physical examination showed her general condition to be good. Typical tetany was present and the Chvostek and Trousseau signs were easily elicited. There was evidence of some loss of hair but no evidence of cataract or dental deficiency. The thyroid was just palpable. Her laboratory data aside from the calcium study were normal. Her blood calcium was 5 mg. and phosphorus 10 mg. per 100 c.c. The spinal fluid calcium was 4.5 mg. The alkaline reserve was 54.6 per cent. With the administration of 20 units of parathormone daily the blood calcium rose to 10.8 mg. and the phosphorus fell to 5.2 mg. in 17 days. She was discharged on a high calcium diet, calcium gluconate and viosterol but the parathormone was omitted. At the next menstrual period she was again in difficulty with tetany and epilepsy and she was readmitted to the hospital.

Between May 1932 and February 1933 the patient had four hospital admissions during which many investigations were conducted. We also followed her in the Out-Patient Department and kept a close record of her calcium metabolism. A summary of the findings follows. The gastric analysis, gastrointestinal roentgen-rays, and barium enema were normal. The basal metabolism averaged minus 5.1 per cent to plus 4.5 per cent. Roentgen-rays of the skull, the long bones, the ribs, and the teeth were normal. The sugar tolerance was normal. The routine blood chemistry was

\* Received for publication June 12, 1939.

From the Department of Medicine, Long Island College of Medicine, and the Long Island College Hospital.

protein, since administration of the incomplete hydrolysate (without addition of the two amino acids) did not raise the plasma protein, and the amino acids were not stored since the nitrogen was rapidly excreted.

More recently Elman and Weiner<sup>6</sup> reported the administration of this mixture by intravenous injection in several human cases of hypoproteinemia and edema. The edema was lessened or relieved; in most cases plasma proteins were increased, and nitrogen balance was restored. No appreciable reactions were observed. From the standpoint of practical therapeutics this procedure is obviously in the earliest experimental stage, but the results warrant the hope that it may eventually be established on a practical basis.

As expressed by Whipple et al.:<sup>3</sup> "Perhaps the most significant concept which derives from all these experiments is the fluidity of the body protein (including the plasma protein)—a ready give and take between the protein depots—a 'dynamic equilibrium' of body protein."

P. W. C.

<sup>6</sup> ELMAN, R., and WEINER, D. O.: Intravenous alimentation, with special reference to protein (amino acid) metabolism, *Jr. Am. Med. Assoc.*, 1939, cxii, 796-802.

phorus 6.9 mg. At this time it was decided to use a new drug, dihydrotachysterol—also known as AT10. Eight ounces of a 5 per cent calcium lactate solution were given daily. With an average dose of 1.5 c.c. of dihydrotachysterol daily the blood calcium rose to 8.7 mg. and the phosphorus fell to 4.6 mg. in six days. On the twelfth day of therapy the menstrual period began and the blood calcium dropped to 7.9 mg.; the phosphorus was unchanged. The dose of dihydrotachysterol was increased to 3 c.c. daily for two days and then dropped to 2 c.c. daily. By the end of the menstrual period on the seventeenth day of therapy the blood calcium was 10.3 mg. and the phosphorus 4.69 mg. During this period the patient felt well and she learned to get around without any fear of calamity. On the nineteenth day she returned home and has continued to do well. She not only takes care of her own home and child, but has even been able to partake of physical exertion such as skating. The medication has consisted of six ounces of 5 per cent calcium lactate solution and 20 minims of dihydrotachysterol daily.\* During the menstrual period the dihydrotachysterol is increased to 21 minims. Her diet has been a full one, including milk, cheese, meats and vegetables. On April 26, 1939, two days after her last menstrual period, the blood calcium was 9.5 mg. and the phosphorus 5.5 mg. We have asked the patient to reduce the milk and cheese in her diet in order to lower the blood phosphorus.

#### COMMENT

It was felt that the patient was suffering from idiopathic parathyroid insufficiency with tetany. The convulsive seizures were due to the low blood calcium allowing a marked irritability of the nervous system to occur. At no time did the patient have a convulsion when the blood calcium was 7 mg. or over. Greenwald and Gross<sup>3</sup> observed that calcium excretion was decreased after parathyroidectomy. In parathyroid deficiency the calcium apparently leaves the blood to be deposited in the tissues,<sup>4</sup> perhaps the bones. In the reported cases no increased density of the bones was observed, but roentgen-rays may not be sufficiently delicate to show the increased deposit of calcium. The occurrence of the symptoms at the time of the menstrual period brought up the question of the influence of the internal secretion of the ovary on the calcium level. The experimental work of Luckhardt and Goldberg<sup>5</sup> showed that there was a physiological antagonism between the ovaries and the parathyroids. These workers treated completely parathyroidectomized dogs with sufficient calcium lactate to prevent tetany but the animals showed a recurrence of all the symptoms of tetany at the time of oestrus. More recently Mathieu<sup>6</sup> has shown that in thyroparathyroidectomized dogs with intact ovaries, the injection of a gonadotropic substance from the urine of pregnant women produced typical oestrus. At the same time there was a marked reduction in the blood calcium and severe tetany ensued. In certain cases the tetany was manifested for as long as 15 days after the injections. In thyroparathyroidectomized dogs without ovaries the injection of gonadotropic substance did not reduce the blood calcium. It also was without influence in the thyroparathyroidectomized male dog and in normal dogs.

Holtz<sup>7</sup> described tachysterol as one of the products of the irradiation of ergosterol. It is less toxic than the others. A dihydro derivative, dihydrotachysterol has a marked effect in elevating the blood calcium. It is not antirachitic. The drug is available in the form of a clear oily solution which is stable indefinitely and is administered by mouth. Its action is similar to parathyroid extract

\*The patient has continued this routine and the last blood study on July 11, 1940 revealed a blood calcium of 9.5 mg. and a phosphorus of 3.63 mg.



without cross reference. Certainly more complete editing would have better coordinated the efforts of the various authors, reduced the size of the volumes, and prevented repetition.

Opinion as to completeness must be deferred until the publication of volumes 3 and 4. Treatment of syphilitic infections of the central nervous system is not discussed in the chapter on syphilis; presumably it will be taken up in one of the two later volumes. The chapter on pulmonary tuberculosis omits discussion of the indications for phrenicotomy and thoracoplasty, and neglects entirely the erythrocyte sedimentation rate as a guide to treatment.

In general, however, there can be no doubt that "The Therapeutics of Internal Diseases" is a valuable publication, containing a wealth of useful and important information. The reviewer looks forward with anticipation to its completion in the near future.

T. N. C.

*Brucellosis in Man and Animals.* By I. FOREST HUDDLESON, D.V.M., M.S., Ph.D., and contributing authors. 339 pages; 15.5 × 23.5 cm. Commonwealth Fund, New York. 1939. Price, \$3.50.

Internists will find this excellent monograph very helpful. It is clearly written, definite in its statements, and covers the field very adequately.

The bacteriologic section will assist the clinical pathologist in improving the laboratory aids to diagnosis. At present in most hospitals, even of major size, attempts to cultivate *Brucella* are relatively perfunctory. The discussion of the serologic, allergic and opsonocytophagic tests includes material on methods and interpretation of great value to the internist. It may be noted in connection with cultural methods that no point is made of the danger of laboratory infections.

Clinical descriptions of the disease in humans are given separately for the American form, by A. V. Hardy, and for the disease as seen in Malta, by J. E. Debono. Both are excellent though it would appear that more detail might be helpful concerning certain aspects. In particular the localizations of *Brucella* in certain foci, though mentioned, are not discussed from the point of view of the variations in clinical course which are observed in such cases. The effects of removing a gall-bladder infected with *Brucella* are occasionally dramatic.

Under differential diagnosis might have been included certain other puzzlingly similar conditions such as for example the Pel Ebstein type of fever in abdominal Hodgkin's disease.

There is a discussion of brucellosis in mammals which will be very informative to the medical reader.

The Commonwealth Fund greatly assists the profession by making it possible to obtain such a valuable monograph at a reasonable price.

M. C. P.

*Convalescent Care:* Proceedings of the Conference Held under the Auspices of the Committee on Public Health Relations of the New York Academy of Medicine. 261 pages; 16 × 23.5 cm. New York Academy of Medicine, New York. 1940.

Medical students often wonder at the system which devotes weeks of care in hospital to a decompensated heart case and discharges him to work for a living, suffer a relapse and return to the hospital. Graduate physicians have too often come to accept such illogical and wasteful use of medical facilities. However, today there is widespread interest in the development of chronic hospitals and of convalescent homes for the treatment of patients requiring institutional medical care of less elaborate nature but of greater length than can be given in the general hospital.

## EDITORIAL

### PLASMA PROTEINS

UNTIL recently, relatively little has been known as to the significance and real function of the plasma proteins. The part they play in maintaining the osmotic pressure within the vessels and in regulating the exchange of fluid between the capillaries and the tissue spaces has been established. It has long been known that the globulin of the plasma includes the various immune bodies active in combating infection, as well as the fibrinogen and the prothrombin concerned in blood coagulation. It was widely assumed that they did not enter directly into the metabolism of the body tissues generally. Their source and the mechanism of their formation has also been in dispute.

Much new light has been shed on some phases of this problem by recent investigations: such as those of Weech at Columbia, Melnick and Cowgill at Yale and, particularly, of Whipple and his associate at Rochester.<sup>1</sup> These studies have been carried out mainly on animals which have been largely depleted of their body proteins by protein starvation or by bleeding. The method employed by Whipple and his associates<sup>2</sup> is particularly ingenious and fruitful. They kept dogs on a standard diet containing approximately a minimum maintenance protein ration. By repeatedly bleeding the animals and restoring the red cells (washed and suspended in salt solution, plasma-pheresis) to avoid producing an anemia, they were able to deplete the plasma proteins to any desired degree. They could maintain this diminished plasma protein level by adjusting the volume of plasma removed. They found that after this procedure had been kept up for several weeks, the amount of plasma which had to be removed to maintain the state was practically constant for the animal. Dogs in which the plasma proteins were thus kept at a constant level of 4 per cent were clinically normal in every other respect. The effect upon plasma protein formation which might be caused by alterations of, or additions to the diet or by other experimental procedures could be measured by the change in volume of bleedings required to maintain this constant level.

To synthesize protein the body requires proteins (or protein split products) from outside sources. The effectiveness of various foods was determined by adding them to the diet of such depleted dogs. As might be anticipated, there was considerable variation in potency. Much the most effective was beef serum, which might result in the production of plasma protein

<sup>1</sup> An excellent review, with bibliography is given by: MADDEN, S. C., and WHIPPLE, G. H.: Plasma proteins: their source, production, and utilization, *Physiol. Rev.*, 1940, xx, 194-217.

<sup>2</sup> MADDEN, S. C., GEORGE, W. E., WARAICH, G. S., and WHIPPLE, G. H.: Blood plasma protein regeneration as influenced by fasting, infection and diet factors; variable reserve stores of plasma protein building material in dog, *Jr. Exper. Med.*, 1938, lxxvii, 675-690.

# COLLEGE NEWS NOTES

## GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following reprints to the College Library of publications by members:

- Dr. Walter H. Baer (Associate), Manteno, Ill.—1 reprint;
- Dr. Nathan Blumberg, F.A.C.P., Philadelphia, Pa.—1 reprint;
- Dr. Dwight T. Bonham (Associate), Hempstead, N. Y.—1 reprint;
- Dr. J. Bailey Carter (Associate), Chicago, Ill.—3 reprints;
- Dr. B. Earl Clarke, F.A.C.P., Providence, R. I.—1 reprint;
- Dr. Joseph F. Elward (Associate), Washington, D. C.—1 reprint;
- Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill.—6 reprints;
- Dr. Alvin G. Foord, F.A.C.P., Pasadena, Calif.—13 reprints;
- Dr. Ernest E. Hadley, F.A.C.P., Washington, D. C.—1 reprint;
- Dr. M. Coleman Harris, F.A.C.P., New York, N. Y.—1 reprint;
- Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—1 reprint;
- Dr. Samuel Morrison, F.A.C.P., Baltimore, Md.—2 reprints;
- Dr. Emma S. Moss (Associate), New Orleans, La.—7 reprints;
- Dr. Frederick W. Mulrow, F.A.C.P., Cedar Rapids, Iowa—1 reprint;
- Dr. Bruce R. Powers (Associate), Knoxville, Tenn.—1 reprint;
- Dr. Harold L. Rakov (Associate), Kingston, N. Y.—1 reprint;
- Dr. John C. Ruddock, F.A.C.P., Los Angeles, Calif.—3 reprints.
- Lt. Col. Seymour C. Schwartz, F.A.C.P., (MC), U. S. Army—1 reprint;
- Dr. John W. Shuman, Sr., F.A.C.P., Los Angeles, Calif.—1 reprint;
- Dr. E. B. Winnett, F.A.C.P., Des Moines, Iowa—1 reprint.

## SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

The following Boards have announced schedules of their examinations as follows. For further details and application forms communicate with the respective secretaries.

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| <p>AMERICAN BOARD OF INTERNAL MEDICINE:<br/>William S. Middleton, M.D., Secretary<br/>1301 University Avenue<br/>Madison, Wis.</p>            | <p>Written Examination, October 21, 1940.<br/>Oral Examination, Philadelphia, December, 1940.<br/>Written Examination, February 17, 1941.<br/>Oral Examination, Boston, April, 1941, in connection with meeting of the American College of Physicians.<br/>Oral Examination, Cleveland, June, 1941, in connection with meeting of the American Medical Association.</p> |
| <p>AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY:<br/>C. Guy Lane, M.D., Secretary<br/>416 Marlboro Street<br/>Boston, Mass.</p>              | <p>Written Examination, October 28, 1940.<br/>Oral Examination, Chicago, December 6-7, 1940.<br/>Applicants in Group B take both the written and oral examinations; applicants in Group A take the oral examination only.</p>   |
| <p>AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY:<br/>Walter Freeman, M.D., Secretary<br/>1028 Connecticut Ave., N. W.<br/>Washington, D. C.</p> | <p>New York City, December 18-19, 1940.</p>   |

special type of protein which might be regarded as storage protein has been isolated. The liver has been regarded as a probable storage site. This view receives some support from the experiments of Addis, Poo and Lew,<sup>4</sup> who studied the amount of protein lost by various organs and tissues in starved rats. They found that the liver lost a larger proportion of its protein (40 per cent in seven days) than any other tissue, and that half of this was given up during the first two days. Conversely, when protein was fed, the concentration in the liver rose more rapidly and to a greater degree than in other tissues.

However, the amount of protein that can be withdrawn from the tissues in acutely depleted starving dogs may be greater than the total protein content of the liver, and it is obvious that other tissues participate in the process.

The nature of the stored material is not known. It seems improbable that it is in the form of simple amino acids. Some must be stored as plasma protein itself, since a substantial amount may be discharged into the plasma within an hour or two in an acutely depleted dog. A large part, however, is yielded up much more slowly; in fact, it appears to be no more promptly available than proteins in the food. It is thought, therefore, that it exists in some other form and requires resynthesis before it is available to the plasma. On the other hand the essential cellular proteins which may be regarded as part of the structure of the cells apparently do not contribute to the replenishment of plasma protein. Formation of the latter ceases in a depleted starved dog, although the nitrogenous by-products of cellular protein breakdown continue to be excreted in the urine. The body can not conserve these by-products and utilize them for new protein formation.

The importance of adequate stores of protein in maintaining normal health and nutrition indicates the advisability of supplying protein parenterally, along with carbohydrate and electrolytes, in patients who can not take them by mouth. This can be accomplished by the intravenous administration of homologous plasma since, as noted, it maintains nitrogen equilibrium in a starving animal, replenishes the reserve stores and raises the plasma proteins to normal. The protein, however, may pass out of the plasma into the tissues until the needs of the cells have been satisfied.

Recent work of Elman,<sup>5</sup> however, indicates that the body needs may be supplied by simpler materials. He subjected casein to hydrolysis, and to this added tryptophane and cystine or methionine, which were scanty or lacking in the hydrolysate. Injection of this mixture into dogs depleted by bleeding or starvation accelerated the restoration of plasma proteins. The nitrogen was retained, and nitrogen balance was restored. Presumably, the amino acids in the hydrolysate were utilized in the synthesis of new

<sup>4</sup> ADDIS, T., POO, L. J., and LEW, W.: The quantities of protein lost by the various organs and tissues of the body during a fast, *Jr. Biol. Chem.*, 1936, cxv, 111-116.

<sup>5</sup> ELMAN, R.: Intravenous injection of amino acids in regeneration of serum protein following severe experimental hemorrhage, *Proc. Soc. Exper. Biol. and Med.*, 1937, xxxvi, 867-870.

Dr. Paul P. McCain, F.A.C.P., Sanatorium, N. C., was elected President and Dr. J. Burns Amberson, Jr., F.A.C.P., New York, one of the Vice Presidents of the National Tuberculosis Association at the annual meeting in Cleveland in June. Surgeon General Thomas Parran, F.A.C.P., U. S. Public Health Service, was made an Honorary Vice President of this organization.

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Dr. Constantine F. Kemper, F.A.C.P., Denver, recently addressed the Northeast Colorado Medical Society on "Pernicious Anemia and Recent Advances in the Treatment of Ductless Gland Disorders."

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Dr. Tomás Cajigas, F.A.C.P., Washington, was recently decorated with the Order of Carlos J. Finlay at a reception at the Cuban Embassy in Washington.

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Dr. Robert M. Moore, F.A.C.P. and College Governor for Indiana, was the guest speaker at a recent meeting of the Gibson County (Ind.) Medical Society, Princeton, his subject being, "The Heart at Middle Age."

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One of the annual Henry Russel awards at the University of Michigan, Ann Arbor, was recently given to Dr. Frank H. Bethell, F.A.C.P., Ann Arbor, for his "direction of field studies of anemias of pregnancy in Hillsdale County," in co-operation with the W. K. Kellogg Foundation.

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Dr. Julius H. Hess, F.A.C.P., Chicago, discussed "Prematurity" and "Bronchiectasis in Childhood" at a symposium on Obstetrics and Pediatrics in Roaring Gap, N. C., June 16-17, held under the auspices of the State Board of Health and the postgraduate committee of the Medical Society of the State of North Carolina.

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Dr. Harry L. Alexander, F.A.C.P., St. Louis, was one of the guest speakers at the annual spring clinic of the Providence (R. I.) Hospital Intern Alumni Association. Dr. Alexander presented a paper on "Physical Examination of the Patient, Stressing Emphysema."

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Dr. Harold M. Coon, F.A.C.P., Statesan, Wis., and Dr. Frank L. Jennings, F.A.C.P., Indianapolis, Ind., were among those who spoke at a series of ten one-day institutes on diseases of the chest, under the sponsorship of the Wisconsin Anti-Tuberculosis Association, the committee on chest diseases of the state Medical Society of Wisconsin, the State Board of Health and the Wisconsin sanatoria.

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Among the guest speakers at the recent annual meeting of the Wyoming State Medical Society, held in Sheridan, were the following:

Dr. Kenneth D. A. Allen, F.A.C.P., Denver, "Practical Considerations of Certain Diseases of the Cervix Uteri with Relation to Prevention of Cancer";

Dr. Peter T. Bohan, F.A.C.P., Kansas City, Mo., "Arthritis: Special Reference to Etiology and Management";

Dr. Charles Douglas Deeds (Associate), Denver, "Recent Advances in the Treatment of Heart Disease."

## REVIEWS

*Carbon Monoxide Asphyxia.* By CECIL K. DRINKER, M.D., D.Sc. 276 pages; 16 × 24 cm. Oxford University Press, London. 1938. Price, \$4.50.

As a reference book for internists and a manual for industrial physicians, this book serves an excellent purpose. Carbon monoxide poisoning is frequent and as an acute emergency calls on the physician for prompt action based on accurate knowledge. Its sequelae are highly varied.

Few subjects have been better elucidated by research, and though many phases are still obscure, the physiologic and biochemical aspects, when presented as clearly as in this book, give to the reader a satisfying sense of complete understanding.

The monograph is written from a practical point of view and includes thorough discussion of the sources of carbon monoxide poisoning, statistical data, the problem of chronic exposure, the confusing subject of chronic poisoning and its effects, and a valuable chapter on treatment. In this last there is an account of the various methods of artificial respiration which is of great interest.

M. C. P.

*The Therapeutics of Internal Diseases.* Volumes I and II. Edited by GEORGE BLUMER, M.A., M.D.; Associate Editor, ALBERT J. SULLIVAN, M.D. Volume I: 872 pages; 25 × 17 cm. Volume II: 1042 pages; 25 × 17 cm. D. Appleton-Century Co., Inc., New York City. 1940. Price, \$10.00 each volume.

These two volumes make up the first half of the projected set; the third and fourth volumes are to be published later in the current year. The publisher intends to present supplementary volumes in the future, at approximately \$3.00 each, whenever advances or changes in therapeutic methods warrant additions to the work.

Volume 1 is general in its scope, including chapters on dietetics, climatology, spa therapy, physical therapeutic methods and their application, radiation therapy and occupational therapy. The chapter on the use of gases, by A. L. Barach, is especially interesting and helpful. Other chapters outline the general principles of endocrine treatment, the use of serums and vaccines, non-specific therapy, bacteriophage, and treatment in psychiatric problems.

The second section of this volume introduces special methods of therapeutic technic, oral and rectal medication, parenteral, intradermal, hypodermic, intramuscular and intravenous therapy, and ends with chapters on blood transfusion, spinal puncture, and paracentesis.

The first section of volume 2 (pages 3 to 458) is made up of two comprehensive chapters on pharmacology and toxicology by Louis S. Goodman. These chapters are interesting and well organized. Section 2 (pages 461 to 481) outlines some general principles of caring for the patient, including management of the convalescent and chronically ill. Section 3 (pages 485 to 969) takes up the management of the infectious diseases.

It is, of course, very difficult to present an accurate description of this comprehensive work in a brief review. Some adverse criticism might be suggested, particularly in reference to the lack of adequate cross editing of the different sections. For example the chapter on pneumonia, by Maxwell Finland, in volume 2, does not mention the discussion of the therapeutic use of gases by Barach, in volume 1, nor the article on the pharmacology of sulfapyridine in a different section of the same volume. Serum treatment of pneumonia is discussed in detail in volume 1, in the general article on serum therapy, and also in volume 2, in the chapter on pneumonia,

- Dr. Edwin G. Bannick, F.A.C.P., Seattle, "Newer Procedures in the Treatment of Pneumonia";
- Dr. Cassius H. Hofrichter, F.A.C.P., Seattle, "Clinical Evaluation of Standard Protamine Zinc and Crystalline Insulin."
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The nineteenth annual meeting of the American Congress of Physical Therapy was held in Cleveland, September 2-6. Among the speakers at this meeting were:

- Dr. Theodore G. Klumpp, F.A.C.P., chief of the drug division, U. S. Food and Drug Administration, "Application of the New Food, Drug and Cosmetic Act to Therapeutic Devices";
- Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn., "Treatment of Diseases of the Peripheral Blood Vessels";
- Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., "Present Status of Ultraviolet Irradiation."
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Dr. R. H. Sundberg, F.A.C.P., San Diego, has been elected President, Dr. Harold G. Trimble, F.A.C.P., Oakland, Vice President and Dr. E. Richmond Ware, F.A.C.P., Los Angeles, Secretary, of the California Tuberculosis Association.

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The American Psychiatric Association held its first regional institute on post-graduate psychiatric education at the Agnew State Hospital, Agnew, Calif. Among those who participated in the institute were:

- Dr. S. Spafford Ackerly, F.A.C.P., Professor of Psychiatry, University of Louisville School of Medicine, Louisville, Ky.;
- Dr. Wendell S. Muncie (Associate), Associate Professor of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Md.;
- Dr. Walter L. Treadway, F.A.C.P., Assistant Surgeon General, U. S. Public Health Service, now stationed at the University of California Medical School, San Francisco.
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The Colorado State Medical Society held its seventieth annual session at Glenwood Springs, September 12-14. Among the speakers at this meeting were:

- Dr. Nathan B. Van Etten, F.A.C.P., New York, President of the American Medical Association, "An American Health Program";
- Dr. Tom Douglas Spies, F.A.C.P., Cincinnati, "Vitamin Therapy in Deficiency Diseases";
- Dr. Charles Douglas Deeds (Associate), Denver, "Recent Advances in the Diagnosis and Treatment of Heart Disease."
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Dr. John Walker Moore, F.A.C.P., Dean and Professor of Medicine at the University of Louisville School of Medicine, Louisville, Ky., received the honorary degree of Doctor of Science from Davidson College, Davidson, N. C.

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Dr. Elliott P. Joslin, F.A.C.P., Clinical Professor of Medicine, Emeritus, Harvard University Medical School, Boston, received the honorary degree of Doctor of Science from Harvard University recently.

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Dr. S. Bernard Wortis, F.A.C.P., New York, has been made Associate Professor of Neurology at New York University College of Medicine.

The proceedings of this well planned conference held in New York in 1939 are a major contribution to the relatively scant literature of convalescent care. The first session was devoted to general basic considerations, physiologic, psychologic, nutritional, etc. Then convalescent care for patients after various diseases was discussed. This group of papers contains many of great interest. The psychosomatic aspects of convalescence were presented at the third session and in the fourth the social, financial and administrative aspects of convalescent care were dealt with in six papers. The last session was given over to a summarization of the conference.

The book is stimulating reading to all internists and especially valuable to those who may be called on to assist their community in a wise development of its medical facilities.

M. C. P.



Courses consist of lectures and clinical demonstrations, stressing the diagnosis and treatment of the various disease conditions.

301—*Arthritis and Rheumatic Diseases*

Two months; 9:00 a.m. to 12:00 m., Tuesdays; Fee, \$35.00.

303—*Cardiology*

Two months; 2:00 to 5:00 p.m., Mondays; Fee, \$35.00.

304—*Clinical Interpretations of Laboratory Data*

Two months; 9:00 to 11:00 a.m., Wednesdays; Fee, \$25.00.

307—*Diagnosis*

Two months; 9:00 a.m. to 12:00 m., Mondays; Fee, \$35.00.

308—*Diseases of the Chest*

Two months; 9:00 a.m. to 12:00 m., Thursdays; Fee, \$35.00.

309—*Diseases of the Thyroid and Other Endocrine Glands, and Obesity*

Two months; 9:00 a.m. to 12:00 m., Fridays; Fee, \$35.00.

310—*Diseases of the Liver and Biliary Tract*

Two months; 11:00 a.m. to 1:00 p.m., Wednesdays; Fee, \$25.00.

311—*Gastro-enterology*

Two months; 2:00 to 5:00 p.m., Wednesdays; Fee, \$35.00.

312—*Clinical Hematology*

Two months; 3:00 to 4:00 p.m., Fridays; Fee, \$15.00.

313—*Diabetes Mellitus and Nephritis*

Two months; 2:00 to 5:00 p.m., Thursdays; Fee, \$35.00.

315—*Psychological Aspects of Internal Medicine*

Two months; 4:00 to 5:00 p.m., Fridays; Fee, \$15.00.

318—*Pulmonary Tuberculosis*

Two months; 9:00 a.m. to 12:00 m., Saturdays; Fee, \$35.00.

319—*Peripheral Vascular Diseases*

Two months; 2:00 to 4:00 p.m., Tuesdays; Fee, \$25.00.

335—*Electrocardiography*

Two two-hour sessions weekly for four weeks; 9:00 to 11:00 a.m., Tuesdays and Thursdays; October 29–November 26, 1940, and April 1–24, 1941; Fee, \$75.00.

344—*Advanced Electrocardiography*

Two two-hour sessions weekly for four weeks; 9:00 to 11:00 a.m., Tuesdays and Thursdays; December 3–26, 1940, and April 29–May 22, 1941; Fee, \$100.00.

*Full-time Courses*

300—*Seminar in Internal Medicine*

Two months; Fee, \$125.00 for one month; \$200.00 for two months.

330—*Arthritis and Rheumatic Diseases*

Five days; September 30–October 4, 1940, and April 14–18, 1941; Fee, \$35.00.

AMERICAN BOARD OF RADIOLOGY:  
B. R. Kirklin, M.D., Secretary  
102 Second Ave., S. W.  
Rochester, Minn.

Boston, September 26-29, 1940.  
Cleveland, June, 1941, at meeting of  
American Medical Association.

AMERICAN BOARD OF PATHOLOGY:  
F. W. Hartman, M.D.  
Secretary-Treasurer  
Henry Ford Hospital  
Detroit, Mich.

Cleveland, June, 1941 in connection with  
the meeting of the American Medical  
Association.

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Dr. M. A. Ogden, F.A.C.P., has been appointed Director of Laboratories and Pathologist to the Passaic (N. J.) General Hospital.

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The Golden Clinic, Elkins, W. Va., presented their sixth annual scientific program August 31. Dr. Pat Alexander Tuckwiller, F.A.C.P., Charleston, presided at a sectional luncheon of the West Virginia Heart Association and Dr. Staige Davis Blackford (Associate), Charlottesville, Va., presented a paper on "Present Concepts of the Therapy of Peptic Ulcer and Gall Bladder Disease" at this meeting.

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Dr. L. J. Moorman, F.A.C.P., Oklahoma City, has been made President, Dr. Harold G. Trimble, F.A.C.P., Oakland, Calif., President-Elect, Dr. Victor F. Cullen, F.A.C.P., State Sanatorium, Md., Vice President and Dr. Benjamin L. Brock, F.A.C.P., Waverly Hills, Ky., Secretary-Treasurer of the American Trudeau Society.

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Dr. Charles A. Doan, F.A.C.P., Columbus, was reelected President and Dr. Henry Kennon Dunham, F.A.C.P., Cincinnati, was elected one of the Vice Presidents of the Ohio Public Health Association at its annual meeting in Cleveland, June 5.

Dr. Herbert R. Edwards, F.A.C.P., New York, was the guest speaker at this meeting, his subject being, "Revitalizing the Tuberculosis Control Problem."

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Dr. Charles L. Brown, F.A.C.P., has been appointed Visiting Physician in the medical wards of the Philadelphia General Hospital, to succeed the late Dr. David Riesman, F.A.C.P.

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Among the speakers at the annual meeting of the Rhode Island Medical Society in Providence in June were the following:

- Dr. Robert F. Loeb, F.A.C.P., New York, "Adrenal Insufficiency and Its Present-Day Management";
  - Dr. Elliott P. Joslin, F.A.C.P., Boston, "Incidence of Diabetes in Rhode Island and Other States";
  - Dr. Clifton B. Leech, F.A.C.P., Providence, "Luetic Heart Disease in Rhode Island."
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Dr. Ramón M. Suarez, F.A.C.P. and College Governor for Puerto Rico, San Juan, was one of the speakers at a recent meeting of the Mayaguez District Medical Society at Yauco, P. R. Dr. Suarez spoke on "Treatment of the Asthmatic Status."

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Dr. Harry E. Ungerleider, F.A.C.P., New York, spoke on "Cardiac Arrhythmia" at a recent meeting of the American Life Convention in Colorado Springs.

The matriculant may supplement the course by an additional six weeks of actual work in the wards and outpatient department of the hospital.  
Dates and fees not announced.

### *Pediatrics*

This institution is prepared to offer two courses in this field, one in general pediatrics and one in endocrine diseases and disorders of infants, children and adolescents.

Dates of the courses and fees were not announced.

### *Dermatology and Syphilology*

#### 140—*Practical Instruction in Dermatology and Syphilology*

Six weeks; dates and fees not announced.

#### 141—*Advanced Course in Dermatology and Syphilology*

Three months; dates and fees not announced.

#### 142—*Syphilology*

Six weeks; dates and fees not announced.

### *Gastro-enterology*

#### 170—*Combined Course in Proctology, Gastro-enterology and Allied Subjects*

Six weeks; dates and fees not announced.

#### 173—*Clinical Gastro-enterology, for the General Practitioner*

Six weeks; dates and fees not announced.

### *Neuropsychiatry*

A general course is announced, though dates and fees are not given.

### *Pathology and Bacteriology*

#### 182—*Blood Transfusions*

A short course; dates and fees not announced.

### *Roentgenology*

#### 190—*Practical Roentgenological Interpretation and Technic*

Three months, or shorter courses by special arrangement; dates and fees not announced.

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## University of Pennsylvania Graduate School of Medicine

George H. Meeker, Ph.D., Dean

36th & Pine Streets

Philadelphia, Pa.

This institution does not schedule short intensive courses, but offers basic study courses in the major clinical departments. A fee of \$800.00 is required for the basic studies in any one of the major clinical departments. There are no fees for continuation studies leading to the Master's and Doctor's degrees for candidates who have previously paid fees for underlying basic clinical studies. When the Master's degree is conferred, for continuation clinical and thesis studies, there is a graduation fee of \$100.00. All the following basic study courses require eight months and are given from October to June annually: internal medicine, pediatrics, neurology-psychiatry, dermatology-syphilology, radiology.

The Graduate School of the University of Pennsylvania also sponsors "personal courses," designed to furnish to physicians relatively brief opportunities for mis-

Dr. Oscar G. Costa-Mandry, F.A.C.P., San Juan, has been elected vice president of the General Anti-Tuberculosis Association of Puerto Rico.

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Dr. Wingate M. Johnson, F.A.C.P., Winston-Salem, N. C., received the honorary degree of Doctor of Science at the recent commencement at Wake Forest College.

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The Utah State Medical Association held its annual meeting in Ogden, August 29-31. Among the guest speakers at this meeting were the following:

Dr. James G. Carr, F.A.C.P., Chicago, "Obscure Fever; Clinical Diagnosis of Coronary Occlusion";

Dr. James F. Churchill, F.A.C.P., San Diego, "Diagnosis and Management of Heart Irregularities; Congestive Heart Failure."

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Dr. Donald A. Palmer (Associate), Spokane, Wash., has been installed as President of the Pacific Northwest Medical Association.

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Dr. Henry H. Turner, F.A.C.P., Oklahoma City, spoke on "Present Status of Endocrinology in General Practice" at the fifth Harlow Brooks Memorial Navajo Clinical Conference held at the Sage Memorial Hospital, Ganado, Ariz., August 26-28.

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Under the auspices of the Iowa State Department of Health and the State University of Iowa College of Medicine, a three-day postgraduate course on the care of the newborn was held at the University Hospital, Iowa City. Among the lecturers were:

Dr. Julius H. Hess, F.A.C.P., Professor of Pediatrics, University of Illinois College of Medicine, Chicago;

Dr. Horton R. Casparis, F.A.C.P., Professor of Pediatrics, Vanderbilt University School of Medicine, Nashville.

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Dr. Henry Kennon Dunham, F.A.C.P., Cincinnati, who recently retired as Medical Director of the Hamilton County (Ohio) Tuberculosis Sanatorium, was honored at a dinner given by the Christmas Seal Committee of Cincinnati and Hamilton County, of which he is President, the Cincinnati Anti-Tuberculosis League, the faculty of the University of Cincinnati College of Medicine and the staff of the Sanatorium.

Dr. Paul P. McCain, F.A.C.P., Sanatorium, N. C., was one of the speakers at the banquet.

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Dr. Henry J. John, F.A.C.P., Cleveland, was one of the speakers on the scientific program at the meeting of the Tenth Councilor District of the Medical Society of the State of Pennsylvania in Pittsburgh, July 17.

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Among the speakers at the scientific session of the fifty-first annual meeting of the Washington State Medical Association, held at Tacoma, Wash., August 25-28, were the following:

Dr. Kenneth K. Sherwood (Associate), Seattle, "Indications and Contraindications for Gold, Vitamin C, Sulfanilamide and Thiamine Therapy for Chronic Arthritis";

opportunities must be acceptable to the heads of the departments in which they wish to work; qualified candidates must enroll for periods of three academic quarters of two months each as a minimum, and preferably for a complete academic year; these opportunities for study are chiefly in the clinical departments, where the graduates will assist in the care of outpatients, doing a certain amount of laboratory study and occasionally undertaking an investigation in the history rooms or in the clinics and laboratories; courses of study are largely individualized, according to needs of candidate; fee, \$50.00 each academic quarter.

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New York Medical College  
Claude A. Burrett, M.D., Dean  
5th Ave. at 105th St.  
New York, N. Y.

*Plan A:*

Opportunities for systematic training, leading to a graduate degree and extending over a period of three years, are offered to approved physicians who wish to qualify for practice in such clinical specialties as medicine, pediatrics, radiology and other branches; in order to qualify for a graduate degree candidates must satisfactorily complete three sessions or periods of study, each of approximately a year's duration—one year as a non-resident fellow devoted to theory and fundamentals, and two years in clinical practice and research as a hospital resident; candidates must pass oral and written examinations and satisfy all other requirements, including the completion of a research problem.

The bulletin outlines specific courses leading to the degree of Master of Science in Medicine in *Internal Medicine*, *Pediatrics* and *Radiology*, as well as some of the surgical specialties. The education committee is convinced that those who successfully complete these courses will be prepared for examination by the various American Specialty Boards.

Matriculation fee, \$10.00; tuition fee, first session, \$400.00; no fee when in residency; graduation fee, \$35.00.

*Plan B:*

Short courses by various College and Hospital departments to provide opportunities for practicing physicians to become familiar with new methods and technics; not credited toward a degree.

*Electrocardiography*—David Scherf, M.D., in charge.

Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, \$100.00.

*Clinical Cardiology*—David Scherf, M.D., in charge.

Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, \$100.00.

*Tuberculosis*—George Ornstein, M.D., and Staff.

May 1–31, 1941; fee, \$100.00.

*Physical Diagnosis*—Herbert Elias, M.D., in charge.

Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, \$100.00.

*Clinical Hematology*—Louis Greenwald, M.D., in charge.

Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, \$100.00.

The sixty-sixth annual meeting of the Oregon State Medical Society was held in Eugene, Ore., September 4-7. Among the speakers at this meeting were:

- Dr. Fred M. Smith, F.A.C.P., Iowa City, "Diagnosis and Treatment of Coronary Artery Disease; Cardiac Therapy; Prognosis and Treatment of Rheumatic Heart Disease";
- Dr. Hans Lissner, F.A.C.P., San Francisco, "Indications for and Proper Use of Synthetic Male Hormone, Testosterone Propionate; Newer Synthetic Female Sex Hormone Preparations, Stilbestrol and Estradiol Dipropionate and Their Administration; Obesity and Leanness";
- Dr. Blair Holcomb, F.A.C.P., Portland, "Education of the Diabetic Patient."
- Dr. Homer P. Rush, F.A.C.P., Portland, was one of those who offered a symposium on "Fluid Administration by Parenteral Methods."
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Under the sponsorship of the Department of Preventive Medicine, the Medical College of Virginia, Richmond, presented a two-day symposium on Industrial Health, September 12-13. Among the speakers were:

- Dr. Bayard T. Horton, F.A.C.P., Rochester, Minn., "Peripheral Vascular Disease in Industry";
- Dr. George H. Gehrmann, F.A.C.P., Wilmington, Del., "Objectives of Health Examinations and Their Industrial Applications."
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Dr. D. G. Preston (Associate), Lewisburg, W. Va., was elected one of the Vice Presidents of the West Virginia State Medical Association at their meeting in White Sulphur Springs, July 29-31.

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#### POSTGRADUATE FACILITIES IN INTERNAL MEDICINE AND ALLIED SUBJECTS

The Board of Regents of the American College of Physicians has directed the publication in the "Annals of Internal Medicine," from time to time, of announcements relating to available educational opportunities in Internal Medicine and the allied specialties, particularly from the standpoint of postgraduate courses.

An attempt has been made, by communicating with the deans of all medical schools in the United States and Canada and with organized postgraduate meetings and societies, to collect all available data. Unfortunately the Executive Office has been unable to obtain replies from all these agencies, and, in some instances, when replies have been forwarded the information is somewhat incomplete. The following announcement of postgraduate courses and postgraduate meetings, therefore, will be supplemented in future reports. For greater detail, consult the institutions.

#### *Part I—Graduate Institutions*

Columbia University  
New York Post-Graduate Medical School and Hospital  
Irving S. Wright, M.D., Executive Officer  
301 E. 20th Street  
New York, N. Y.

#### *Part-time Courses:*

A number of courses in the field of medicine are offered three times during the year, beginning with the week of October 1, 1940, January 2, 1941 and April 1, 1941.

Stanford University School of Medicine  
L. R. Chandler, M.D., Dean  
2398 Sacramento St.  
San Francisco, Calif.

This institution conducts postgraduate medical courses for practicing physicians in coöperation with the San Francisco Department of Public Health and the San Francisco Hospital; courses of one-week duration are given each year and those for 1940 have already been completed; bulletin listed pediatrics, gastro-enterology, management of hypertension and nephritis, roentgen-ray diagnosis and therapy.

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Tufts College Medical School, Postgraduate Division  
Samuel Proger, M.D., Chairman  
30 Bennet St.  
Boston, Mass.

This institution will offer the following courses during the fall of 1940. In addition to the tuition fee noted under each course, there is a \$5.00 registration fee. This fee covers all courses taken within a twelve-month period.

*Electrocardiography*—September 16-21.

To familiarize the general practitioner, through demonstrations and intensive study of records, with the present status of electrocardiogram interpretation. An advanced course will be given in January for those who have satisfactorily completed this course. Dr. Heinz Magendantz in charge. Fee, \$25.00.

*Hematology A*—October 21-26.

Mornings are spent at staff conferences and on laboratory and clinic work in the Joseph H. Pratt Diagnostic Hospital and Boston Dispensary. In the afternoons there are case presentations and lectures on the following subjects: bone marrow; anemia (pernicious, iron deficiency, and hemolytic); leukopenic disorders; leukemia. Dr. Heinrich G. Brugsch and Dr. William Dameshek in charge. Fee, \$25.00.

*Allergy*—October 28-November 2.

The course is intended, through clinic demonstrations and lectures, to familiarize the general practitioner with the present-day status of the diagnosis and treatment of allergic conditions. Dr. Ethan Allan Brown in charge. Fee, \$25.00.

*Diseases of the Chest*—October 28-November 2.

Teaching ward rounds and clinics will be held at the Corey Hill and Deaconess Hospitals, the Norfolk County Sanatorium, and the Boston Dispensary. Lectures and demonstrations will be given in the Joseph H. Pratt Diagnostic Hospital. Dr. Richard H. Overholt in charge. Fee, \$25.00.

*Radiology*—November 11-16.

The course is intended to familiarize the general practitioner with the fundamentals of x-ray interpretation. The attempt is made to consider all the systems of the body in the study of which x-ray is of prime importance. Dr. Alice Ettinger in charge. Fee, \$25.00.

*Cardiology*—November 25-30.

The course will emphasize the practical application of present-day knowledge of heart disease. Throughout the course therapy of heart disorders will receive especial attention. Dr. Samuel Proger in charge. Fee, \$25.00.

- 331—*Allergy*  
Three weeks; December 2–20, 1940, and April 14–May 2, 1941; Fee, \$150.00.
- 332—*Cardiovascular Diseases*  
Four weeks; March 3–29, 1941; Fee, \$125.00.
- 333—*Diseases of the Chest including Tuberculosis*  
Ten days; October 21–November 1, 1940; Fee, \$50.00.
- 334—*Endocrinology*  
Ten days; October 7–18, 1940, and March 3–14, 1941; Fee, \$50.00.
- 336—*Gastro-enterology*  
Three weeks; September 9–28, 1940, and March 3–22, 1941; Fee, \$75.00.
- 337—*Diabetes Mellitus, Nephritis and Hypertension*  
Five days; November 11–17, 1940, and April 21–25, 1941; Fee, \$35.00.
- 338—*Therapeutics*  
Five days; December 2–6, 1940; Fee, \$35.00.
- 340—*Peripheral Vascular Diseases*  
Five days; December 9–13, 1940; Fee, \$35.00.
- 341—*Symposium in Medicine*  
Ten days; June 9–20, 1941; Fee, \$30.00 for five days; \$50.00 for ten days.
- 342—*Physical Diagnosis*  
Ten days; January 13–24, 1941; Fee, \$50.00.
- 345—*Electrocardiography*  
Five days; October 14–18, 1940; Fee, \$100.00.
- 347—*Clinical Interpretations of Laboratory Data*  
Five days; June 2–6, 1941; Fee, \$35.00.
- 348—*Tropical Medicine*  
Five days; May 19–23, 1941; Fee, \$50.00.
- 350—*Pulmonary Tuberculosis*  
Four weeks; May 1–29, 1941; Fee, \$100.00.
- 351—*Symposium on the Clinical Applications of Chemotherapy and Vitamins*  
Five days; February 24–28, 1941; Fee, \$35.00.
- In addition to these part-time and full-time courses, the New York Post-Graduate Medical School has scheduled similar courses in neurology and psychiatry, pathology, pediatrics, bacteriology, dermatology and syphilology.

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New York Polyclinic Medical School and Hospital  
F. H. Dillingham, M.D., Medical Executive Officer  
341–53 W. Fiftieth Street  
New York, N. Y.

#### 110—*Medicine*

Full-time Course; six weeks; integrated clinical and didactic study; fundamental theories applied in clinic; practical problems in diagnosis and treatment; demonstrations in medical specialties, including cardiology, allergy, arthritis, tuberculosis, diabetes and metabolism, gastro-enterology, pediatrics, neuropsychiatry and dermatology and syphilology.



meet the requirements of the active physician in general practice and to avoid the discussion of the subjects in a highly specialized manner; round table discussions; therapeutics; bedside instruction; fee, \$50.00.

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University of California Medical School  
M. S. Marshall, M.D., Acting Dean  
San Francisco, Calif.

*Dermatology*

January 6-8, 1941; fee, \$20.00; an intensive refresher course on the clinical aspects of dermatology; given at the University of California Hospital.

In June, 1941, another refresher course will be given, but subject and announcements referring thereto will come later.

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University of Chicago, Division of the Biological Sciences  
c/o Dean of Students, Biological Division  
Chicago, Ill.

1. *Advanced GastroscoPy*

Course given under supervision of Dr. Schindler; limited to one student per College quarter; course offered during the summer, autumn and winter quarters; fee, \$150.00.

2. *GastroscoPy*

Two weeks, repeated each month at definite periods; fee, \$100.00; course under direction of Dr. Schindler; registration limited to three physicians; applicants requested to indicate on their applications what special preparation or experience they have had in this field; arrangements for the course usually should be made many months in advance.

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University of Georgia School of Medicine  
G. Lombard Kelly, M.D., Dean  
Augusta, Ga.

By special arrangement with the Head of the Department of Medicine, the University of Georgia School of Medicine will receive for training a limited number of physicians who may desire postgraduate training in internal medicine. Arrangements for such training may be made with the Professor of Medicine.

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University of Illinois  
1853 W. Polk St.  
Chicago, Ill.

This institution offers no short intensive courses in internal medicine, but does offer graduate work leading to the Master's Degree in Medicine, based on research and advanced study; further details to be secured from the Recorder.

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University of Michigan Medical School  
A. C. Furstenberg, M.D., Dean  
Ann Arbor, Mich.

The Department of Postgraduate Medicine of the University of Michigan announces the following annual postgraduate courses for the spring of 1941:

cellaneous studies in subdepartmental subjects. Academic credits are not involved. Fees for personal courses are arbitrary, and are not affected by the total hours, or time periods, involved in actual work.

#### TABULATION OF PERSONAL COURSES

*Cardiology*—William D. Stroud, M.D., Professor of Cardiology.

8 Thursdays, 52 hours, courses beginning the first Thursday of October, January and April; Fee, \$80.00.

*Parasitology and Tropical Medicine*—Damaso deRivas, M.D., Professor of Parasitology.

6 weeks, 150 hours; Fee, \$125.00.

*Clinical Gastro-enterology*—H. L. Bockus, M.D., Professor of Gastro-enterology.

16 weeks, 500 hours; Fee, \$400.00.

*Allergy*—H. B. Wilmer, M.D., Associate Professor of Allergy.

4 weeks, 40 hours; Fee, \$150.00.

*Diabetes Mellitus*—Edward S. Dillon, M.D., Assistant Professor of Diseases of Metabolism.

2 to 4 weeks, 75 hours; Fee, \$150.00.

*Clinical Psychiatry*—S. DeW. Ludlum, M.D., Professor of Psychiatry.

8 weeks, 240 hours; Fee, \$160.00.

*Clinico-biologic Neurology and Psychiatry*—D. W. Bronk, Ph.D., Professor of Neurology; Earl D. Bond, M.D., Professor of Psychiatry; and Associates.

10 weeks, 250 hours; Fee, \$100.00.

#### *Part II—Other Medical Colleges*

Boston University School of Medicine

Alexander Begg, M.D., Dean

750 Harrison Ave.

Boston, Mass.

Boston University School of Medicine offers the following courses in cardiac diagnosis:

*Clinical Electrocardiography*—James M. Faulkner, M.D.

*Cardiac Roentgenology*—George Levene, M.D.

Teaching clinics will be held at the Massachusetts Memorial Hospitals and will consist of twelve sessions of two hours each on Wednesdays from 10:30 a.m. to 12:30 p.m. from October 2 to December 18. Fee, \$50.00 for one course; \$75.00 for both courses.

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Johns Hopkins University School of Medicine

Alan M. Chesney, M.D., Dean

710 N. Washington St.

Baltimore, Md.

No specific schedule of formal graduate courses is offered. However, the School of Medicine offers to a limited number of graduates in medicine opportunities for study in the various departments. Candidates desiring to avail themselves of these

*Pediatrics*

This course, contributed by the American Academy of Pediatrics, consists of lectures and clinics on those conditions in infancy and childhood which contribute prominently to mortality and disability. Three days; no registration fee.

*Diagnostic Roentgenology. III. The Skeletal System including the Skull*

This is the third in a series of courses in diagnostic roentgenology. This course will be limited in scope to roentgen consideration of the skeletal system including the skull. No instruction in roentgen technic will be offered. One week; fee, \$10.00.

*Internal Medicine*—Courses designed to prepare candidates for national specialty board examinations.

Courses are arranged in internal medicine and most of its subdivisions for indeterminate periods for those desiring special training. While exceptions may be made, these courses are primarily designed for those who have had the preliminary training required by the national specialty boards. Each course is arranged individually to take advantage of the large amount of pathological material, the anatomical and chemical laboratories, as well as the special departments in hematology, arthritis, serology and psychiatry. Fee, \$25.00 per month.

The program of this institution also calls for a number of postgraduate courses to be given during the summer of 1941, including courses in biological chemistry, dermatology and syphilology, internal medicine, clinical microscopy, neurology, pathology, autopsies, and medical roentgenology.

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University of Virginia  
H. E. Jordan, M.D., Dean  
University, Va.

*Postgraduate Clinics*

During the session this University gives two postgraduate clinics, one in the autumn and one in the spring; these clinics are designed primarily for the practitioners of the State; specific dates not given; no registration fee.

*Recent Advances in Internal Medicine*

The above course was given June 17 to 22, 1940, and the intention has been expressed of giving the course again during June, 1941; fee, \$15.00.

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University of Wisconsin Medical School  
William S. Middleton, M.D., Dean  
Madison, Wis.

In addition to the opportunities in residencies and research fellowships, the University of Wisconsin Medical School has made the following announcement:

Observation courses have been organized by the Medical Faculty and Staff of the State of Wisconsin General Hospital upon the approval of the Regents of the University of Wisconsin. No stereotyped courses or lectures are afforded, but attendance upon lectures, clinical services and staff meetings of the Hospital is arranged. A stated fee is charged all physicians in attendance upon the clinical services for periods exceeding one (1) month. This fee shall be \$100.00 per month or \$400.00 per semester and shall be credited to the department to which the physician is assigned. A certificate of attendance shall be granted upon the completion of the course and shall be signed by the President, Dean of the Medical School and chief of the responsible department. No credit toward an advanced degree may be earned

*Management of the Diabetic*—Thomas H. McGavack, M.D., in charge.

Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, \$100.00.

*Endocrinology*—Thomas H. McGavack, M.D., in charge.

Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, \$100.00.

All courses given at New York Medical College and Metropolitan Hospital, except Tuberculosis, which will be given at Metropolitan and Sea View Hospitals.

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New York University College of Medicine

Currier McEwen, M.D., Dean

477 1st Ave.

New York, N. Y.

*Graduate Study of Medicine*—three-year full-time course.

A limited number of recent graduates in medicine who have had at least two years' internship or its equivalent will be admitted to this course in internal medicine; problems pertaining to the basic medical sciences as applied to clinical medicine are developed by the students under the guidance of a member of the faculty and in conjunction with other departments, according to the nature of the study; fee, \$12.00 for each year of work.

### *Short Courses*

#### *Internal Medicine*

Five mornings per week for a period of one month; each month constitutes a complete session; eight sessions during the year, from October through May; fee, per session, \$50.00.

Course designed for physicians in general practice desiring a practical review of recent advances in diagnosis and treatment; instruction will be given to small groups.

#### *Clinical Electrocardiography*

Fifteen weeks, 2:30 to 4:30 p.m., Mondays; October 7, 1940–January 13, 1941, and February 3–May 12, 1941; fee, per session, \$50.00.

Interpretation of the electrocardiogram and its practical application; measurement and analysis of a large number of curves; operation of standard instruments; normal and abnormal electrocardiograms; Louis F. Bishop, Jr., M.D., Director; courses given by the Fourth Medical Division of Bellevue Hospital.

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Northwestern University

J. Roscoe Miller, M.D., Director of Courses

303 E. Chicago Ave.

Chicago, Ill.

This institution conducts postgraduate courses in gastro-enterology, cardio-renal-vascular medicine, endocrinology and hematology by short intensive courses of from six to twelve days, with fee of \$25.00 for one-week courses and fee of \$50.00 for two-week courses; late August and early September schedule already completed; no announcement at hand for repetition of these courses later in year.

### 5. *Graduate Course in Internal Medicine*

This course consists of supervised work with patients in the medical outpatient service, including the related specialties; experience in the diagnostic laboratories; assigned reading, seminars and conferences, including pathological and radiological conferences and autopsy study; directed study and seminars in the pre-clinical sciences, particularly physiology and biochemistry. Special investigation of a particular problem in one of the divisions of internal medicine as the basis of a thesis is required. The course extends over a period of one year and is open to physicians who have completed an internship, have had an additional year's experience as assistant resident in medicine or its equivalent and are acceptable to the school. Courses begin July 1 and are limited to six students. Tuition fee, \$300.00.

#### *Fellowships*

Three fellowships are available for this course described above. These fellowships, which provide tuition, board and lodging, are open to those who meet the requirements mentioned above and will be awarded on the basis of the individual's training and recommendations.

### 6. *Special work in the Department of Medicine may be made available by special arrangement.*

Tuition and fees according to arrangement.

Further information regarding these courses should be addressed to the Registrar of the School of Medicine, Vanderbilt University, Nashville, Tenn.

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Woman's Medical College of Pennsylvania  
Dr. Margaret D. Craighill, Acting Dean  
Henry Ave. & Abbottsford Rd.  
East Falls, Philadelphia, Pa.

This institution offers but one postgraduate course. This is an intensive course of two weeks' duration in electrocardiographic technic given during the summer months, if five registrants are obtained. Fee, \$100.00.

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Yale University School of Medicine  
333 Cedar St.  
New Haven, Conn.

Any physician of good standing in the community may on application to the head of a department in the Yale University School of Medicine obtain permission to attend clinics, lectures, conferences or ward rounds; or to do special work in association with the laboratories connected with the various departments. The institution lists opportunities for observation in medicine, pediatrics, psychiatry, pathology, public health, child development and the surgical specialties, giving hours of ward rounds, staff conferences, seminars, demonstrations, etc. There are no formally organized postgraduate courses announced.

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#### *Part III—Postgraduate and Clinical Meetings*

The American College of Physicians  
4200 Pine St.  
Philadelphia, Pa.

A group of one and two week intensive postgraduate courses will be scheduled immediately preceding the Annual Session of the College at Boston, April 21-25, 1941.

*Gastro-entecrology*—December 2-7.

This course is designed to familiarize the general practitioner with modern methods of examination of the gastro-intestinal tract, as well as with the diagnosis and treatment of gastro-intestinal disease. The clinical and laboratory facilities of the Boston Dispensary and the Joseph H. Pratt Diagnostic Hospital furnish ample material for demonstration and informal discussion. Dr. Katherine S. Andrews in charge. Fee, \$25.00.

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Tulane University of Louisiana School of Medicine  
Maxwell E. Lapham, M.D., Dean  
1430 Tulane Ave.  
New Orleans, La.

*Annual Clinic Week, October 7-12, 1940*

Registration fee, \$5.00.

Open to all licensed practitioners of medicine; consists of all-day lectures, demonstrations and day clinics, covering the entire field of medicine and its branches.

*Review Courses*

Review courses are designed largely for general practitioners, but offer a rather comprehensive review for anyone who has been unable to keep abreast of the literature.

*The Medical Review Course*

Four weeks, January 6 to February 1, 1941; fee, \$100.00.

Course in medicine includes pediatrics and some radiological interpretation.

*Tropical Medicine and Parasitology*

September 30, 1940, to February 7, 1941; course designed to equip physicians for the practice of medicine in the tropics.

Throughout the year Tulane University arranges on demand part-time intensive instruction in certain subjects such as cardiology, pediatrics, cystoscopy, etc.

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University of Arkansas School of Medicine  
Stuart P. Cromer, M.D., Dean  
Little Rock, Ark.

The postgraduate committee of the Arkansas State Medical Society, in connection with the University, will give a two-day general postgraduate course in Little Rock October 16-17, 1940; internal medicine will not be featured exclusively, but there will be some refresher courses offered in physical diagnosis and other subjects in the field of internal medicine.

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University of Buffalo School of Medicine  
Edward W. Koch, M.D., Dean  
24 High St.  
Buffalo, N. Y.

*20th Annual Session—Course for general practitioners*

September 16-28, 1940.

A course designed to acquaint general practitioners with the advances brought forth each year in medicine, surgery, obstetrics and the specialties; review of fundamental subjects in connection with clinical problems; designed to

Omaha Mid-West Clinical Society  
1036 Medical Arts Bldg.  
Omaha, Nebr.

The 8th Annual Assembly of the Omaha Mid-West Clinical Society will be held in Omaha, Nebr., at the Paxton Hotel, October 28 to November 1, 1940.

This society is made up of one hundred and twenty-five active members, all located in Omaha and all members of the faculty of the medical school of either Creighton University or Nebraska University. The membership is divided into sections according to specialties. Among the sections are medicine, pediatrics, neuropsychiatry, radiology, dermatology, and the basic sciences. This Assembly will offer five days of intensive graduate study presented by a distinguished group of from fifteen to seventeen guest speakers. Each will give two addresses and one clinic. One day of the meeting will be devoted to a symposium on the anemias, discussed by Drs. Frank H. Bethell, Ann Arbor, Mich.; George M. Curtis, Columbus, Ohio; Willis M. Fowler, Iowa City, Iowa; Frank J. Heck, Rochester, Minn.; and Roy R. Kracke, Decatur, Ga. A local lecture program will be presented by forty-eight active members of the society. Annual dues of active members, \$10.00; \$5.00 registration fee paid by all attending the Assembly.

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Philadelphia County Medical Society  
21st & Spruce Sts.  
Philadelphia, Pa.

The 6th Annual Postgraduate Institute of the Philadelphia County Medical Society, under the direction of Rufus S. Reeves, M.D., will be held in Philadelphia at the Bellevue-Stratford Hotel, March 31 to April 4, 1941. The subject of this Postgraduate Institute will be "Symposia on Modern Therapy," and will cover immunology, pediatrics, dermatology, gastroenterology, physiotherapy, allergy, chemotherapy, the avitaminoses, x-ray therapy, pneumonia and upper respiratory infections, the acute infections, and gynecology. The program will be made up of speakers whose work is authoritative, who are members of the various medical schools, and who are members of the Philadelphia County Medical Society.

All members of a county medical society in good standing are eligible for registration. Fee, \$5.00.

### *Allergy*

Course in clinical phases of allergy offered to a limited group; taught mainly by demonstrations; includes study of asthma, hay fever, food allergy, eczema, contact dermatitis and dust sensitization, with methods of recognition and treatment. The practical aspects and office management of these conditions are emphasized. The course is arranged so that the entire field of allergy can be presented over a period of successive years. One week; fee, \$10.00.

### *Diseases of Blood and Blood-Forming Organs*

Course consists of a comprehensive review of the present knowledge of the blood, its physiology, embryology, and pathology. Clinical and laboratory studies are made of a selected group of patients. Standard laboratory methods are demonstrated and analyzed, and special features, as bone-marrow puncture, blood transfusion, etc., are considered. The course is planned to enable the physician to obtain a better understanding of the status of blood-forming organs and to select the most adequate treatment for his patients. One week; fee, \$7.50.

### *Diseases of the Heart*

Clinical aspects of heart disease are stressed in this short intensive course. Instruction includes examination of patients and practical demonstrations of cases. References for study in advance of the course are suggested. Three days; fee, \$5.00.

### *Electrocardiographic Diagnosis*

This course consists of lectures with lantern slides and demonstrations, and the examination under supervision of a large number of electrocardiograms from the files of the laboratory. One week; fee, \$25.00.

### *Nutritional and Endocrine Problems*

This course is planned to acquaint the practitioner with the fundamental principles of metabolism. The phenomenal advances in biological chemistry and clinical investigation have gone far to explain a number of disease conditions which either have not been understood or for which there was no satisfactory treatment. These conditions include diabetes mellitus, nephritis and edema, obesity, deficiency diseases, gout, and dysfunctions of the parathyroid and the adrenal glands. Material will be presented by means of lectures, demonstrations, and selected reading. One week; fee, \$7.50.

### *Pathology*

Four intensive courses, especially arranged for postgraduate students, are offered during the summer session. These courses are as follows:

*Special Pathology of Neoplasms:* Histopathological diagnosis of neoplasms with special emphasis on rare forms. Discussion on diagnosis, treatment, and prognosis. Laboratory open all day. Demonstration, 3-5 p.m. daily. Two weeks; fee, \$15.00.

*Pathology of the Female Genito-Urinary Organs:* This course deals with the microscopical pathology of the female genito-urinary tract, with special emphasis upon neoplasms of both external and internal genitalia. The more important infections are illustrated in their various situations and special attention is paid to the interpretation of endometrial curettings. Laboratory open all day. Demonstration 3-5 p.m. daily. Two weeks; fee, \$15.00.

*Special Pathology of the Eye:* Laboratory open all day. Demonstration, 3-5 p.m. daily. Two weeks; fee, \$15.00.

*Special Pathology of the Ear, Nose, and Throat:* Laboratory open all day. Demonstration, 3-5 p.m. daily. Two weeks; fee, \$15.00.



He was a Fellow of the American College of Physicians and American Medical Association, a member of the International Union Against Tuberculosis, the American Climatological Association, the American Association of Thoracic Surgery, the Society of Thoracic Surgeons, the Mississippi Valley Tuberculosis Association, the Radiological Society of North America, the American Public Health Association, the Michigan State Medical Society, and the Michigan Trudeau Society.

Dr. Pritchard had unusual organizing ability which was recognized by Mr. W. K. Kellogg who chose Dr. Pritchard as head of the W. K. Kellogg Foundation, which position he held to the time of his death. Under Dr. Pritchard's guidance the Foundation established health departments in seven counties; it also assisted schools in these same counties. It provided tuition in universities and psychiatric clinics for groups of teachers, supervisors, school board members, ministers, newspaper editors, physicians, nurses, dentists and veterinarians.

Dr. Pritchard recognized that a policy of patronage would fail where a program of participation and coöperation would succeed; as a result the Foundation is doing a remarkable work.

CHARLES E. STEWART, M.D., F.A.C.P.

### DR. JOHN A. LANFORD

Dr. John A. Lanford, F.A.C.P., of New Orleans, La., who was born in Gainesville, Ala., June 19, 1881, died July 2, 1940.

In the passing of Dr. Lanford, the medical profession of Louisiana has lost one of its most distinguished members and the College has suffered an irreparable loss.

In the Louisiana State Medical Society, he rendered most valued service as a member of the Journal Committee, which shapes and controls the policies of the official journal of the Society.

As Chairman of the Cancer Committee of the Louisiana State Medical Society since 1932, he accomplished much in the way of enlisting the members of the profession in the work of cancer control, as well as educating the public regarding what everybody should know about cancer.

He was educated in his native state, receiving a Ph.G. degree from Alabama Polytechnic Institute in 1900, and his M.D. degree from the University of Alabama School of Medicine in 1905. From 1908 to 1910 he was Instructor of Anatomy at the University of Alabama School of Medicine; from 1911 to 1914 he was Instructor of Surgical Pathology, and since 1914, Assistant Professor of Pathology and Bacteriology at Tulane University of Louisiana School of Medicine. He was Pathologist and Director of Laboratories at Touro Infirmary; Pathologist, New Orleans Hospital and Dispensary for Women and Children; and Consulting Pathologist to the U. S. Marine Hospital. He was a member and past president of the Orleans

by such attendance, nor is it purposed to include the existing residencies in the scope of this recommendation.

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Vanderbilt University School of Medicine  
John B. Youmans, M.D., Department of Medicine  
Nashville, Tenn.

### 1. *Medicine*

These courses, which are designed primarily for the holders of Commonwealth Fund fellowships, are given during the summer from approximately mid-June to mid-July. The course is of one month's duration and consists of seminars, conferences and practice work in the wards and the outpatient department in Internal Medicine and allied specialties of dermatology, neurology, psychiatry, metabolic diseases, allergy, diseases of the chest and syphilis.

It is designed to review this field for the general practitioner and acquaint him with the advances in diagnosis and treatment. A limited number of physicians in addition to the holders of Commonwealth Fund fellowships will be accepted under certain conditions. Tuition, \$50.00.

### 2. *Syphilis—Medicine 12. For County Health Officers and Physicians with Appointment in Public Health Units*

This course is open to county health officers and physicians with appointments in public health units. It is designed to familiarize the health officer with all aspects of the syphilis problem. It offers him the opportunity of studying the individual patient, history taking, physical examination, darkfield and lumbar puncture procedures and treatment.

The student attends each clinic session for a period of four weeks and assists in the conduct of the clinic. A series of lectures early in the course is given to review the clinical and epidemiological aspects of syphilis. The remainder of the time is devoted to field work, under the direction of the epidemiologist. Several such courses are given from September to April inclusive. Each course is limited to six physicians. No tuition fee.

### 3. *Syphilis—Medicine 13. Postgraduate Course in Syphilis*

This course is open to properly qualified physicians wishing to secure special training in syphilis. It is designed to offer training fitting the student for positions of responsibility in syphilis control work.

The physician is expected to take his place as one of the staff of the clinic, to examine and treat his patients, assuming responsibility for them. Opportunity for thorough training is offered in the conduct of a syphilis clinic, the diagnosis of the disease, including darkfield and lumbar puncture procedures and in treatment. Epidemiological field work is to be done under the direction of the epidemiologist of the syphilis clinic.

Physicians will be accepted for such work for a period of six to twelve months, dependent upon the needs of the individual physician. No tuition fee.

### 4. *Syphilis B. Demonstration in Syphilis Clinic Management for Physicians and Nurses*

This course is open to physicians and registered nurses. It is designed to give an opportunity to physicians and nurses to observe the management of patients and clinic procedures for a period of two weeks at intervals during the year. Several such courses are given from September to April inclusive. No more than three physicians and two nurses will be accepted during each period. No tuition fee.

ently. He was fond of teaching and much interested in the younger members of the medical profession. Dr. Wright was indeed an excellent physician, a fine administrator, an important teacher and a valuable friend.

EDGAR VAN NUYS ALLEN, M.D., F.A.C.P.,  
Governor for Minnesota

### DR. JOSEPH CONDIT

Dr. Joseph D. Condit, F.A.C.P., aged 63 years, died at his home in Pasadena on July 5, 1940, following a long illness.

Dr. Condit was educated at Wabash College and was later honored by a Master's degree. He received his medical education at the College of Physicians and Surgeons of Columbia University, where he was graduated in 1901. He began practice in California in 1904 in Pasadena, where he has resided ever since. He was a member of many professional organizations, among which were the Los Angeles County, California State, and American Medical Associations and the American Heart Association. He had been a Fellow of the American College of Physicians since 1920. He was a diplomate of the American Board of Internal Medicine. He was a member of the attending staff of St. Luke's Hospital, and the Medical and Consulting staff of the Huntington Memorial Hospital, and formerly a member of its Board of Directors. During the World War Dr. Condit served as a major in the Medical Corps as regimental surgeon to the 79th Field Artillery. He was later made a Lieutenant-Colonel in the Reserve Corps. He was a member of the Pasadena University Club, and formerly a member of the Valley Hunt Club. Before his illness he enjoyed the activities of a number of social and civic organizations.

Dr. Condit in his long residence in Pasadena had grown up with the city, and was widely and well known by a host of friends who, with his family, feel the great loss they have sustained.

EGERTON L. CRISPIN, M.D., F.A.C.P.,  
Regent.

The Committee on Postgraduate Education, headed by Dr. Edward L. Bortz of Philadelphia, has announced that courses in advanced internal medicine, cardiology, hematology and other associated branches will be given in four or five different centers of the United States during the period April 7-19, 1941. Bulletins and detailed announcements will be issued later.

The Twenty-Fifth Annual Session of the College, covering internal medicine and its allied specialties and consisting of General Sessions, Special Lectures, Panel Discussions, Clinics and Demonstrations, will be held in Boston, April 21-25, 1941, with headquarters at the Statler Hotel.

Dallas Southern Clinical Society  
1133 Medical Arts Bldg.  
Dallas, Texas

The Dallas Southern Clinical Society will hold its 13th Annual Spring Clinical Conference in Dallas at the Hotel Adolphus, March 17-20, 1941. The meeting will consist of general assemblies, postgraduate teaching, clinics, round tables, clinical-pathological conferences, and scientific and technical exhibits. Among the guest speakers in the specialties indicated will be the following:

Dr. C. J. Barborka, Chicago .....	Medicine
Dr. W. Edw. Chamberlain, Philadelphia .....	Radiology
Dr. Harry Goldblatt, Cleveland .....	Pathology
Dr. Henry G. Poncher, Chicago .....	Pediatrics
Dr. Marion B. Sulzberger, New York .....	Dermatology
Dr. Soma Weiss, Boston .....	Medicine

These speakers will appear daily in general assemblies, clinics, and symposia. In addition, local members of the profession will present a series of postgraduate lectures and one afternoon of clinics and symposia.

Any physician who is a member of his county medical society may register. Registration fee, \$10.00.

The New York Academy of Medicine  
2 East 103rd Street  
New York, N. Y.

The 1940 Graduate Fortnight will be held October 14 to 25, 1940. The subject will be "Infections." The program will consist of morning panel discussions, afternoon hospital clinics, evening addresses, scientific exhibits and demonstrations. Registration limited to the medical profession; Fellows of the Academy admitted without fee; all others pay registration fee of \$5.00.

Oklahoma City Clinical Society  
609 Medical Arts Bldg.  
Oklahoma City, Okla.

The 10th Annual Fall Clinical Conference of the Oklahoma City Clinical Society will be held in Oklahoma City at the Biltmore Hotel, October 28-31, 1940. The meeting will consist of general assemblies, postgraduate symposia, round table discussions, and clinics. The program will include many guest speakers from various parts of the country, who are prominent in their own specialties. Registration fee, \$10.00.

entire history of the development of toxoid immunization. Some of the high lights, however, may be briefly mentioned.

The work of active immunization against tetanus can be said to be the direct outgrowth of the method and procedure followed in the battle against diphtheria. The success attained in the fight against diphtheria by active immunization, and the value of alum-precipitated diphtheria toxoid in producing an active immunity, are attested by the complete freedom in some modern cities from the menace of childhood diphtheria.

Both diphtheria and tetanus produce soluble toxins or exotoxins. Both of these exotoxins, treated with formaldehyde and heat, become nontoxic but retain their antigenic power. These detoxified products were first called anatoxin by the French, but since then have been referred to by English-speaking nations as toxoids to avoid confusion with the word antitoxin. Both of these toxoids are precipitated by the use of alum and, though relatively insoluble when injected, gradually go into solution. Thus, antigenic stimulation is exerted little by little and over a long period of time, the recognized principle of secondary stimulation in vaccination thus being automatically employed. Antitoxin, developed as a result of this prolonged, smooth and steady action, is eventually much greater in amount than that produced by several injections of soluble and rapidly diffusible toxoid such as plain formolized toxoid.

It is understandable that immunization against diphtheria and tetanus should be coupled in our minds, because of the similarity mentioned, and because of the fact that both were developed by Ramón in the same laboratory.

Two important differences between diphtheria and tetanus, however, exist, namely: subclinical tetanus apparently does not occur and thus no natural immunity is found to exist; and there is no easy method for gauging immunity against tetanus such as the Schick test in diphtheria.

Our work on active immunization against tetanus in the U. S. Navy began in 1934 on the U. S. S. *Relief*, the fleet hospital ship. At this time the manufacture of toxoid was just beginning in this country. This investigation was designed to gather information on the optimum interval between each toxoid injection and the number of injections required for successful immunization. The study was begun using plain formol toxoid and was completed on some groups in which alum-precipitated toxoid was used exclusively.

Our observations from this study were: (a) that alum-precipitated toxoid was a much more efficient immunizing agent than plain toxoid: that is, it gave uniformly higher serum antitoxin titers; (b) the longer the interval, up to eight weeks, between the alum-precipitated toxoid injections, the better were the results obtained; and (c) that even very hurried immunization, such as at intervals of two weeks, gave quite titratable serum-antitoxin levels. Individuals apparently so poorly immunized by this rapid method

*OBITUARIES*

## DR. STUART PRITCHARD

Stuart Pritchard, M.D., F.A.C.P., aged 58 years, died at his home in Battle Creek, Mich., at 4:45 p.m., Sunday, August 4, 1940. Dr. Pritchard became ill about six months previously. The first indication of his illness manifested itself by a rapid enlargement of the thyroid gland while he and Mrs. Pritchard were spending their vacation at their winter home in Barbados, British West Indies. Sensing the necessity of early medical skill, he came by air to the University Hospital at Ann Arbor, Mich. On April 16 an operation was performed and it was discovered that the enlargement was due to sarcoma of the thyroid, the gravity of which was immediately recognized. Every possible aid that medical and surgical science had to offer was secured, but the disease rapidly progressed until his death.

Dr. Pritchard was born at Auburn, Ont., Canada, in 1882. He secured his degree of Doctor of Medicine from the University of Toronto Faculty of Medicine in 1905. He was one of twelve prominent Americans awarded honorary degrees at the 96th commencement of the University of Michigan last June. At that time the degree of Doctor of Science in Medicine was conferred upon him for "distinguished and outstanding contributions to the field of Medicine and Public Health."

Dr. Pritchard was frequently appointed to positions of responsibility. Last November he participated, by order of the Secretary of State, in an educational conference in Washington, being among two hundred representatives of twenty-one American Republics.

After his graduation in medicine, Dr. Pritchard spent several years associated with Dr. Parfitt at Gravenhurst, Ont., and later with Dr. VonRuck at Asheville, N. C., in the study and treatment of tuberculosis. Soon after this, in 1917, Dr. Pritchard joined the staff of the Battle Creek Sanitarium as Chief of the Chest Department, where he remained in active service for seventeen years. During this period he spent considerable time in presenting papers before medical societies throughout this country and Canada, and gained a national and international reputation as an authority on pulmonary diseases.

In 1928 Dr. Pritchard represented the United States Government at an international conference on tuberculosis at Rome, Italy; and in 1932 he was delegated by the President as the nation's delegate to the Hague Conference of the International Union Against Tuberculosis.

He was honored by the presidency of the leading tuberculosis societies of the nation—the National Tuberculosis Association, the Mississippi Valley Tuberculosis Association, and the Michigan Trudeau Society, of which he was one of the founders.

later, only recently begun to manufacture alum-precipitated tetanus toxoid. This toxoid had a fine physical appearance and had passed all tests for toxicity and antigenicity prescribed by the National Institute of Health.<sup>2</sup> We, therefore, knew that this toxoid, as well as all others licensed by the National Institute of Health, was completely detoxified and would produce no symptoms of tetanus in guinea pigs, even when injected in 10 times the human dose. We also knew that 1 c.c. would, in six weeks, produce, when injected into a 350 gram guinea pig, 2 units of antitoxin per c.c. of serum. In the first injection 2300 men were immunized. The reactions were minor and as noted in table 1.

TABLE I  
Tetanus Toxoid Immunization  
Naval Academy

	1938			1939	
	1st Inj.	2d Inj.		1st Inj.	2d Inj.
	Toxoid (A)	Toxoid (A)	Toxoid (B)	Toxoid (B)	Toxoid (B)
Total Injected	2300	1800	500	793	793
Total Reactions	10	50	None	1	None
Sore arms	8	38	None	0	None
Fever and malaise	2	7	None	1	None
Urticaria	1*	4	None	0	None
Anaphylaxis	0	1	None	0	None

\* One month after injection.

Eight had sore arms; two had fever and malaise; one had urticaria. This urticaria occurred over a week following the injection and was thought to be due to a dietary factor at the time. Subsequently it was thought that perhaps it might not have been, and that it might justly be charged against the toxoid. In the second injection, eight weeks later, 1800 men were injected with Toxoid "A." Reactions were noted from the first, although rather minor in type. Fifty reactions were recorded in total, comprised of 38 sore arms, seven cases of fever and malaise, four of urticaria, and finally one instance of frank anaphylactic shock. The use of this toxoid was promptly stopped and the remaining 500 men were injected with another toxoid. These 500 did not have a reaction of any sort, not even one sore arm! It seems clear from the observations of these results that the Toxoid "A" contained some substance which on the first injection sensitized these men. When, after an interval of eight weeks, 1800 of them were given the second injection of toxoid, a considerable number reacted as noted. This

Parish Medical Society; a member of the American Society of Clinical Pathologists; the American Medical Association; member of the Board of Directors of the American Society for the Control of Cancer; Chairman, Cancer Committee, Louisiana State Medical Society; and a Fellow of the American College of Physicians since 1927.

Personally, Dr. Lanford was a most delightful individual, who will be greatly missed by his many personal friends as well as by many professional admirers.

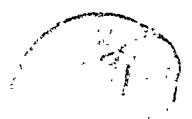
JOSEPH E. KNIGHTON, M.D., F.A.C.P.,  
Governor for Louisiana

### DR. CHARLES BENJAMIN WRIGHT

Charles Benjamin Wright, F.A.C.P., was born in Kemptville, Ontario, Can., November 3, 1876 and died in Minneapolis, Minn., of myocarditis and emphysema on May 31, 1940. He moved to Grand Forks, N. D. with his parents and graduated from the University of North Dakota in 1898. He graduated from the Johns Hopkins University School of Medicine in 1902, following which he was House Officer of the Johns Hopkins University Hospital. After graduate study abroad in Vienna, Berlin and Rome in 1913 and 1914 he was appointed Associate Professor of Medicine at the University of Minnesota Medical School, a position which he held from 1920 to 1935. Dr. Wright had been Professor of Clinical Medicine at the University of Minnesota Medical School since 1935.

He was a member and past president of the Hennepin County Medical Society, member and past president of the Minnesota State Medical Association, member of the Minnesota Pathologic Society, Minnesota Academy of Medicine, Central Society for Clinical Research, Trudeau Society, Minnesota Society of Internal Medicine and a Fellow of the American College of Physicians since 1934. At the time of his death he was chairman of the Executive Committee of the Board of Trustees of the American Medical Association. Dr. Wright was the author of several articles dealing with rectal bleeding, histamine, undulant fever and microcytic anemia.

He was a prominent member of the University of North Dakota football team prior to his graduation and maintained his interest in athletics throughout his life, following with enthusiasm the progress of the University of Minnesota football team, and gaining reputation as a good bowler. Dr. Wright was friendly and loyal to those whom he respected and liked, and demonstrated his friendship at the cost of much time and energy to him. Because of his wide experience in administrative matters, his friends looked to him for advice and counsel in the organization of staffs and in the solution of problems connected with medical societies and hospitals. He was frank in his opinions, but when he disagreed with his associates, he disagreed tactfully with full consideration of the views of those who thought differ-





of protein present. We also ran certain protein tests,\* with results in general as noted in table 2: positive with Toxoid "A," negative with Toxoid "B," and negative with the National Institute of Health toxin.

The evidence just cited suggested that we should be able to sensitize guinea pigs and be able to shock and perhaps produce anaphylactic death by using the toxoid which appeared to contain a sensitizing substance. Rather surprising results were obtained. In the first place the reinjection of alum-precipitated tetanus Toxoid "A" into guinea pigs sensitized by a previous injection of this toxoid produced no anaphylaxis. For this we had no explanation unless there was too small an amount of the substance in soluble form in the supernatant fluid. What was noted is recorded in table 3.

Guinea pigs were injected with alum-precipitated tetanus toxoid. After an interval of time they were injected with another dose of alum-precipitated tetanus toxoid; no reaction occurred. But, when injected with crude tetanus toxoid, pigs from this lot died in anaphylaxis. Could this be due to a broth protein which had been carried over and was producing sensitization? To test this, pigs from the same lot were injected with *crude diphtheria* toxoid from the same type broth; no reaction occurred. Then the picture was reversed; we used a set of guinea pigs sensitized by injecting alum-

\* Reactions for proteins.

Test	Toxin (NIH)	Toxoid "A"	Toxoid "B"	Test specific for:
Biuret reaction	Negative	Weak positive	Negative	(CO.NH <sub>2</sub> ) Carbamyl group
Ninhydrin reaction	Weak positive	Slight positive	Weak positive	Amino-acids, peptides, proteins. All acids having a free amino group in the alpha position.
Glyoxylic acid reaction	Negative	Positive	Negative	Tryptophan nucleus.
Molisch-Udransky reaction	Positive	Positive	Positive	Specific for carbohydrate group.
Hydrochloric acid and heat test	Negative (No color)	Positive (Deep purple)	Positive (No color)	Positive when protein is present with toxoid.

The hydrochloric acid and heat test may represent a new observation. We have not been able to locate such a test in the literature. Credit for this observation should be given Chief Pharmacist P. S. Gault, U. S. Navy. It appears to depend upon the simultaneous presence of a formalized tetanus toxoid molecule and a protein molecule, such as serum albumin. Specimens of toxoid which reacted negatively to this test were mixed with blood serum and used as positive controls.

The washed and dried alum-precipitated tetanus toxoid was treated with concentrated hydrochloric acid to convert it to a water-soluble form. Toxoid "A" dissolved with the formation of a deep purple color; whereas Toxoid "B" dissolved without the formation of the purple color.

Another portion of Toxoid "B," to which blood serum had been added, was treated with concentrated hydrochloric acid; a deep purple color was produced. Prior to the addition of the hydrochloric acid, the dried toxoid-serum mixture was evaporated to dryness on a water bath.

# ANNALS OF INTERNAL MEDICINE

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## TETANUS TOXOID IMMUNIZATION IN THE UNITED STATES NAVY\*

By COMMANDER W. W. HALL, F.A.C.P., *Medical Corps, U. S. Navy*

THE purpose of this paper is to summarize the work on tetanus immunization done in the U. S. Navy since 1934, some of which has previously been reported,<sup>1, 2</sup> and to present a few thoughts concerning the value to the military services of active immunization against tetanus.

The development of toxoid immunization against tetanus is not entirely new. As long ago as 1926 Ramón<sup>3</sup> reported satisfactory immunization of humans using formol toxoid or anatoxin. Work on this subject was confined largely to France for the next few years. Then, on this continent from 1932 to 1936, various papers appeared, reporting on the immunization of animals as well as human beings. Papers were published by Lincoln and Greenwald,<sup>4</sup> Bergey and Etris,<sup>5</sup> Sneath,<sup>6</sup> Sneath and Kerslake,<sup>7</sup> and Hall.<sup>1</sup>

In the last three or four years, as active immunization with tetanus toxoid has been more widely used, the literature upon this subject, both here and in Europe, has grown rapidly.

Toxoid immunization develops active immunity. Active immunization is nature's method of protection. All naturally developed immunity to infectious disease, as well as immunity developed by vaccination, is active immunity. Active immunity is in general persisting immunity. Passive immunity on the other hand, although it may be highly effective under properly controlled conditions, is merely stop-gap or substitution therapy and is temporary in nature.

It is, of course, not necessary to plead the cause of active immunization to the profession today. Nor is it necessary to recount to this audience the

\* Read at the Cleveland meeting of the American College of Physicians April 1, 1940.

Tables 6 to 11 are from the article, "Active Immunization against Tetanus with Tetanus Toxoid," by W. W. Hall, *Nav. Med. Bull.*, 1937, xxxv, 34-41.

Tables 12 to 14 are from the article entitled, "Active Immunization against Tetanus, Using Alum Precipitated Tetanus Toxoid," by R. Hayden and W. W. Hall, *Nav. Med. Bull.*, 1938, xxxvi, 524-535.

TABLE V  
Tetanus Toxoid Immunization  
Titration Naval Academy Immunees  
1937-1940

Group no.	Injection dates			Antitoxin per c.c. serum	
	1st	2d	3d	Date of bleeding 1/20/40	
A-1	4-1-37	6-2-37	9-7-37	>0.05	<0.1
A-2	9-10-37	10-26-37	3-7-38	0.01	0.05
A-3	4-1-37	6-2-37	9-7-37	0.01	0.1
A-4	4-1-37	6-2-37	9-7-37	0.01	0.05
A-5	4-1-37	6-2-37	9-7-37	0.01	0.05
A-6	4-1-37	6-2-37	9-7-37	0.1	
A-7	4-1-37	6-2-37	9-7-37	0.01	0.05
A-8	4-1-37	6-2-37	9-7-37	0.01	0.05
A-9	4-1-37	6-2-37	9-7-37	0.1	0.5
A-10	4-1-37	6-2-37	9-7-37	0.01	0.05
A-11	4-1-37	6-2-37	9-7-37	0.01	0.05
A-12	4-1-37	6-2-37	9-7-37	0.1	
B1-1	9-27-38	12-7-38		0.08	
B1-2	9-27-38	12-7-38		0.5	
B1-3	9-27-38	12-7-38		0.01	0.05
B1-4	9-27-38	12-6-38		0.05	0.1
B1-5	9-29-38	12-6-38		0.07	
B1-6	9-29-38	12-6-38			0.05
B2-1	3-29-38	5-27-38	9-27-38	0.1	0.5
B2-2	3-29-38	5-27-38	9-27-38	0.1	0.5
B2-3	3-5-38	9-10-38	9-27-38	0.01	0.05
B2-4	3-29-38	9-27-38	12-6-38	0.5	
B2-5	3-29-38	5-27-38	9-28-38	0.1	0.5
B2-6	3-29-38	5-31-38	10-10-38	0.1	0.5
C-1	8-17-39	9-23-39		0.1	0.3
C-2	8-15-39	9-21-39		0.05	0.1
C-3	8-17-39	9-23-39		0.8	1.0
C-4	8-17-39	9-23-39		0.1	0.2
C-5	8-17-39	9-23-39		0.1	0.3
C-6	8-15-39	9-21-39		0.1	0.5
C-7	8-15-39	9-21-39		0.3	
C-8	8-15-39	9-21-39		0.1	0.2
C-9	8-17-39	9-23-39		0.1	0.3
C-10	8-17-39	9-23-39		0.5	
C-11	8-17-39	9-23-39		0.4	0.5
C-12	8-15-39	9-21-39		0.1	0.3

or tetanus alum-precipitated toxoid is followed by an injection of the homologous crude toxoid, a sufficient dose of the shock-producing substance is present, in soluble form, to produce a reaction. This conclusion also appears clear: an alum-precipitated toxoid, thoroughly washed, is a safe immunizing agent. Crude toxoid is not, although it should be remembered that that which can produce anaphylactic reactions in guinea pigs does not react with equal severity in man. However, crude toxoid, on second and third injections, may produce reactions of sensitization, while well prepared alum-precipitated toxoid should not.

On further investigation it was found that the alum-precipitated toxoid "A," which had produced reaction in our group in the Naval Academy with the second injection, had been prepared in such a manner that it probably

—surprising to us at that time—when injected with alum precipitated toxoid two to three years later, reacted within seven days with high serum antitoxin.

Another organized study of tetanus immunization in the U. S. Naval service was carried on at the U. S. Naval Academy in 1937 and reported by Hayden and Hall.<sup>2</sup> In this study a group of volunteers, largely football players, were immunized with alum-precipitated toxoid and the sera titrated for antitoxin. It may be interesting to note that the football players volunteered to be immunized against tetanus so that they might avoid the rather frequent serum sickness reactions which had occurred in a number of their fellow teammates after having been spiked on the field. These reactions had kept men out of play for some time and occasionally out of important games. Nine months to a year later these men were given injections of alum-precipitated toxoid and titrated before and after this repeat injection. The outstanding observation in this large group (153) was that no individual failed to respond with an adequate blood level of antitoxin, though, as in the previous *Relief* group, there were rather wide individual variations.

The final and by far the largest group studied is that which is now reported for the first time (table 5), by permission and through the courtesy of Captain R. Hayden, Medical Corps, U. S. Navy, senior medical officer during this period at the Naval Academy where the work was carried on. The entire personnel of the Academy has been immunized for the past three years. The individuals so immunized in the Naval Academy will now total 3,446.

The freedom from reactions in the use of alum-precipitated toxoid has been universally noted. Our observations have been that there is soreness of the arm, disappearing in 48 hours or sooner, from the injections which were given intramuscularly. When injections are made subcutaneously there may be a skin reaction which is greater in intensity the closer to the skin the material is placed. This is followed by a subcutaneous induration which may last, as a nodule, one or two weeks. We have chosen the intramuscular route and have made it routine in our work in the Navy, because of the relative freedom from local reaction experienced when using this route. It has been suggested that immunity is enhanced when the material is placed in the skin. This has not been our observation, for in those who have a violent skin reaction we have failed to observe any uniformly higher level in antitoxin titer than in those in whom the injection was made intramuscularly and in whom there was little or no skin reaction present. General reaction has been, with the exception to be noted later, very minor, seldom amounting to more than some malaise and an occasional minor rise in temperature of short duration.

When immunizing the midshipman personnel of the Naval Academy in 1938, 2300 men were injected. We obtained for this immunization, by purchasing in the open market, a supply of alum-precipitated tetanus toxoid made by one of the well established biological houses which had, it appeared

TABLE VI  
Group I.—*Antitoxin titrations* (U. S. S. Relief)  
[Units per cubic centimeter of serum]

Volunteers no.	A	B	C*	D	E	F
2-I.....	0.01	0.20	0.50	0.04	0.01-0.04	3- 5.0
5-I.....	.01	0.10- .20	1.0	0.10- .25	.01- .25	1.0
6-I.....	.01	.20- .50		.25	.25	5- 8.0
13-I.....	.01	.50-1.0		.50	.50	3- 4.0
15-I.....	.01	.50-1.0	1.00-2.0	.25	.25	5- 7.0
17-I.....	.01	2.0	2.00-3.0	.25	.25	5-10.0
19-I.....	.01	.20- .50	.50-1.0	.10- .25	.10	3.0
24-I.....	.01			.10	.10- .25	3- 5.0
29-I.....	.01	.50-2.0	1.00-2.0			
Average.....	.01	.78	*1.30	.217	.215	4.40

1 cubic centimeter of old toxoid given as "sensitizing" dose, 8 months' rest, then 2 doses of alum-precipitated toxoid with 6-week interval between doses. Titration before each dose (A and B) and 10 weeks after second dose of alum-precipitated toxoid (C\*). Finally 17 months after initial injection or 8 months after third injection, a dose of alum-precipitated toxoid was given with titrations before (D), 2 days after (E), and 7 days after the injection (F).

\* The titration giving the highest average response to the basic immunization is indicated by asterisk (\*).

TABLE VII  
Group II.—*Antitoxin titrations* (U. S. S. Relief)  
[Units per cubic centimeter of serum]

Volunteers no.	A	B	C*	D	E	F	G
11-II.....	0	0.001	0.01-0.20	0.04	0.01-0.04	0.01-0.04	2 -3.0
14-II.....	0	.001	.01- .04	.01- .04	.01- .10	.01	.5-1.0
25-II.....	±	.005	.10	.04- .10			
33-II.....	0	.001	.01- .10	.04- .10			
38-II.....	0		.02		.01	.04	1 -2.0
40-II.....	±	.002	.01- .04				
41-II.....	0	.001	.10	.04- .10	.04	.04	3 -5.0
43-II.....	0		.01	.01- .04	.04	.04	3 -5.0
Average.....	±	.002	*.055	.05	.035	.031	2.550

3 doses (1 c.c. each) of old toxoid; 5-week interval between first and second, and 6-week interval between second and third were given in the basic course.

*Titration.*—A, 5 weeks after first dose (just before second was given); B, 6 weeks after second; C\*, 24 weeks after third; D, 35 weeks after third; E, 17 months after first or approximately 14 months after completion of course of 3 injections. At this time (17 months after first injection) an injection (1 c.c.) of alum-precipitated toxoid was given, following which titrations were made at 2-day interval (F) and 7-day interval (G).

\* The titration giving the highest average response to the basic immunization is indicated by asterisk (\*).

TABLE VIII  
Group II (A).—*Antitoxin titrations* (U. S. S. Relief)  
[Units per cubic centimeter of serum]

Volunteers no.	A	B	C	D
70-II (A).....	0	0.01		0.04-0.10
82-II (A).....	±	.04	0.10-0.20	.10- .25
95-II (A).....	±	0.10- .25	.10- .20	.04- .10
Average.....	±	.070	.15	.10

3 injections (1 c.c. each) of old toxoid; 8-week interval between first and second injections, 6-week interval between second and third.

*Titrations.*—A, 8 weeks after first dose; B, 6 weeks after second dose; C, 19 weeks after third dose; D, 49 weeks after third dose.

supposition was strongly supported when the remaining 500 men were injected with another lot of toxoid and no reaction of any type resulted (table 1).

In 1939 the incoming class of midshipmen were injected. These totaled 793. In the first injection only one reaction was noted, a fever which may or may not have been due to the toxoid. During the second injection of all these 793 men no reaction of any kind occurred. No man reported to the sick-bay for treatment. No man requested to be excused from drill formation or from class. To the medical officers, used to handling midshipmen, this seemed indeed remarkable (1939 section, table 1).

Our study of this reaction-producing toxoid presents some points of interest.

The exact structure of the tetanus toxin molecule is not known. It is, however, known to be an organic nitrogen-containing compound, nonprotein in nature. It appears to act as the deuteroproteoses, since it is precipitable by full saturation with ammonium sulphate. The toxin molecule is large and will not pass through a semi-permeable membrane.

We began our study of the nitrogen content of this reaction-producing toxoid (Toxoid "A") by comparing its nitrogen content with that of protein. It is well known that the nitrogen content of protein is approximately 16 per cent, and that amino acids and the derived proteins, being the building stones of the complete protein molecule, must approximate this 16 per cent nitrogen content. Should tetanus toxin or tetanus toxoid be of protein composition, it would approximate protein in its nitrogen content. It will be noted by reference to table 2 that the nitrogen content of the toxin

TABLE II  
Study of Reaction-Producing Toxoid (A)

	Toxoid (A)	Toxoid (B)	Toxin (N.I.H.)
Organic nitrogen grams %.....	5.5	3.3	5.1
Protein tests.....	Positive	Negative	Negative

obtained from the National Institute of Health was 5.1 per cent. The toxoid which had given reactions on the second injection of 1800 men (Toxoid "A") approximated 5.5 per cent nitrogen. Toxoid "B" which was just as high in antigenic potency as Toxoid "A," and was free from reaction-producing substances, gave a nitrogen value of 3.3 per cent. Our supposition from these nitrogen values, i.e., from the high nitrogen value of Toxoid "A," higher even than the highly potent toxin of the National Institute of Health, and from our clinical observation, was that Toxoid "A" contained a protein substance. As protein contains 16 per cent nitrogen it would, if mixed with the toxoid, raise its nitrogen content in proportion to the amount

TABLE XI  
Group V.—*Antitoxin titrations* (U. S. S. Relief)  
[Units per cubic centimeter of serum]

Volunteers no.	A	B*	C	D	E
108-V.....	0.010	0.10-0.50	0.010-0.040	0.040	3- 5.0
111-V.....	.010	.25- .50	.010- .040	.010	2.0
112-V.....	.010	.25- .50	.040	.010-.04	5- 8.0
117-V.....	.010	1.0	.040- .10	.040	10-15.0
120-V.....	.010	.50-1.0	.040	.040	8.0
121-V.....	.010	.5	.040	.040	8.0
122-V.....	.010	.10- .25	.010- .04	.010-.04	3- 5.0
124-V.....	.010	.50-1.0	.040	.010-.04	15-25.0
129-V.....	.010	.10	.040	.010-.04	5- 8.0
131-V.....	.010	.50-1.0	.010- .04	.010-.04	10.0
133-V.....	.010	.10- .25	.010- .04	.010	1.0-2.0
134-V.....	.010-10	.5	.110	.10	25-50.0
136-V.....	0.1	.25- .50	.010	.010	3- 5.0
Average...	.010	*.40	.039	.032	9.60

Two doses of alum-precipitated toxoid (A.P.T.) with 6-week interval between injections in basic course.

*Titration*s.—A, 6 weeks after first injection; B, 6 weeks after second injection; C, 9 months after first injection and just before the final repeat or stimulation dose of A.P.T.; D, 2 days after repeat dose of A.P.T.; E, 7 days after repeat dose of A.P.T.

\* The titration giving the highest average response to the basic immunization is indicated by an asterisk (\*).

TABLE XII  
Group I—53 subjects (Naval Academy, 1938)  
[Units of antitoxin per c.c. of blood serum]

No.	Titration A	Titration B	No.	Titration A	Titration B
I-1.....	>0.025- <0.05	0.1	I-29.....	.025	.1
I-2.....		.1	I-30.....	>.075- <.1	.25
I-3.....	>.1 - <.15	.75	I-31.....	.025	.1
I-4.....	>.025- <.05	.1	I-32.....	>.1 - <.15	.25
I-5.....	>.075- <.1	.1	I-33.....	>.1 - <.15	>1.0 - <1.5
I-6.....	>.075- <.1	>.75 - <1.0	I-34.....	.025	>.075- <.1
I-7.....	>.075- <.1	.1	I-35.....	.025	.1
I-8.....	>.025- <.05	>.075- <.1	I-36.....	.1	.5
I-9.....	>.05 - <.075	.25	I-37.....	.075	.25
I-10.....	.025	.1	I-38.....	>.1 - <.15	.5
I-11.....	>.075- <.1	>1.0 - <1.5	I-39.....	.075	.25
I-12.....	<.01	>.075- <.1	I-40.....	>.1 - <.15	.75
I-13.....	>.1 - <.15	>.25 - <.5	I-41.....	>.1 - <.15	.75
I-14.....	.025	.25	I-42.....	.075	.25
I-15.....	.025	.1	I-43.....	.075	.75
I-16.....	.025	>.1 - <.25	I-44.....	.1	>1.0 - <1.5
I-17.....	>.05 - <.075	2.0	I-45.....	.025	.1
I-18.....	.05	>.1 - <.25	I-46.....	.1	.5
I-19.....	>.01 - <.025	.1	I-47.....	.025	>.075- <.1
I-20.....	>.075- <.1	>1.0 - <1.5	I-48.....	.075	.1
I-21.....	.025	.1	I-49.....	.1	.5
I-22.....	.05	.5	I-50.....	.075	>.25 - <.5
I-23.....	.075	>.5 - <.75	I-51.....	.05	.5
I-24.....	.05	.1	I-52.....	.025	>.75 - <1.0
I-25.....	>.1 - <.15	>.25 - <.5	I-53.....	>.1 - <.15	>1.0 - <1.5
I-26.....	<.01	>.075- <.1			
I-27.....	.075	>.5 - <.75	Average	.062	.433
I-28.....	.025	.5			

NOTE.—The sign (>) means greater than; and the sign (<) means less than.

TABLE III  
Sensitization of Guinea Pigs with Toxoid

Pigs injected with			
A.P. Tetanus Toxoid	Time Interval	A.P.T. Tetanus Toxoid	No Reaction
A.P. Tetanus Toxoid	Time Interval	Tetanus Toxoid Crude	Death
A.P. Tetanus Toxoid	Time Interval	Diphtheria Toxoid Crude (Same Broth)	No Reaction
A.P. Diphtheria Toxoid	Time Interval	Diphtheria Toxoid Crude	Death
A.P. Diphtheria Toxoid	Time Interval	Tetanus Toxoid Crude (Same Broth)	No Reaction

TABLE IV  
Tetanus Toxoid Immunization  
*Showing follow-up titrations on some 6 year cases*

1-2 (Relief)		
June 1934	—1 dose plain tetanus toxoid.	
Dec. 1934	—2 doses alum precipitated tetanus toxoid. (8 weeks interval)	
Dec. 4, 1935	—Titer, 0.1 unit	
Dec. 5, 1935	—4th dose alum precipitated tetanus toxoid.	
Dec. 12, 1935	—Titer, >3.0 <5.0 units.	
Jan. 4, 1940	—Titer, 0.1 0.5 unit.	
V-117 (Relief)		
Feb. 8, 1935	—2 doses (6 weeks interval) alum precipitated tetanus toxoid.	
Nov. 5, 1935	—Titer, 0.04 unit.	
Nov. 5, 1935	—3rd dose alum precipitated tetanus toxoid.	
Nov. 12, 1935	—Titer, 10.0 15.0 units.	
Jan. 4, 1940	—Titer, 0.5 1.0 unit.	
Jan. 4, 1940	—4th dose alum precipitated tetanus toxoid.	
Jan. 12, 1940	—Titer, 15.0 units.	
V-124 (Relief)		
Feb. 28, 1935	—2 doses (6 weeks) alum precipitated tetanus toxoid.	
Nov. 5, 1935	—Titer, 0.01 unit.	
Nov. 5, 1935	—3rd dose alum precipitated tetanus toxoid.	
Nov. 12, 1935	—Titer, 10.0 15.0 units.	
Jan. 4, 1940	—Titer, .5 1.0 unit.	
Jan. 4, 1940	—4th dose alum precipitated tetanus toxoid.	
Jan. 12, 1940	—Titer, 12.0 units.	
IV-46 (Relief)		
June 1934	—3 doses (6 weeks interval) plain tetanus toxoid.	
June 1936	—Titer, 0.01 unit.	
June 1936	—1 dose alum precipitated tetanus toxoid.	
June 1936	—(7 days later) Titer, 0.25 0.5 unit.	
Jan. 4, 1940	—1 dose alum precipitated tetanus toxoid.	
Jan. 4, 1940	—Titer, 0.3 unit.	
Jan. 12, 1940	—Titer, 10.0 units.	

precipitated diphtheria toxoid. No reaction occurred when these pigs were injected with alum-precipitated diphtheria toxoid but they died of anaphylactic shock when injected with *crude diphtheria* toxoid. Yet no reaction occurred when others from the same lot were injected with *crude tetanus* toxoid from homologous broth. We wish to thank Dr. W. T. Harrison of the National Institute of Health for help in this phase of the study.

These results clearly indicate that alum-precipitated toxoid contains sensitizing and immunizing fractions. If an injection of either diphtheria



TABLE XIV  
Group III—22 subjects (Naval Academy, 1938)  
[Units of antitoxin per c.c. of blood serum]

No.	Titration A	Titration B	No.	Titration A	Titration B
III-131...		0.1	III-144..		>.1- <.5
III-132...		>.1- <0.5	III-145..	.5	
III-133...	>0.05- <0.1	>.1- <.5	III-146..	.05	<.5
III-134...		.5	III-147..		1.5
III-135...	>.1- <.25	1.0	III-148..	.25	.5
III-136...		.1	III-149..	.1	>.5- <1.0
III-137...	<.05	.5	III-150..	>.05- <.1	.5
III-138...	.1	<.5	III-151..	.25	.5
III-139...		.1	III-152..	.05	.5
III-140...	>.05- <.1	1.0	III-153..		1.5
III-141...		>.5- <1.0			
III-143...	.1	1.0	Average	.140	.552

toxin formation and produce it in an ideal manner—progressively as the organisms multiply.

Bergey, Brown and Etris<sup>15</sup> have shown that circulating antitoxin does not measure the total protection, the tissue immunity being considerably greater. They also have demonstrated in animals that 0.01 unit antitoxin per c.c. is amply protective. Even such figures, probably, are not a measure of the minimum protective level; there may be no minimum. "Once immunized always protected" may some day be proved. Dr. W. T. Harrison of the National Institute of Health well expressed the thought that basic tissue immunity, not titratable humoral immunity, is of prime importance when he said (personal communication) "As far as I am aware, there are no figures available which will indicate the antitoxin level necessary to prevent tetanus. The most important factor, it seems to me, is the development of a situation within the body which will permit rapid formation of antitoxin, should it become necessary."

The majority of our titrations, following repeat injections, have been made at the end of one week. This was not done because of the fact that we felt that the antitoxin curve had reached its height at this time but to demonstrate the rapidity of rise of antitoxin. An Ensign, who had been immunized in the Naval Academy, was injured after graduation in an automobile accident which occurred a year and a half after his immunization. We obtained a specimen of blood serum which showed a level of slightly less than 0.1 unit of antitoxin per c.c. He was then injected with 1 c.c. of alum-precipitated tetanus toxoid, and one week later a specimen of blood was obtained. This second specimen showed an antitoxin level of 2 units per c.c. Two months following this, another specimen of blood was obtained, his blood at that time showing an antitoxin level of 12 units per c.c. This observation illustrates the rising curve of antitoxin in those individuals who have a basic or tissue immunity.

was inadequately washed. After throwing down the precipitate in a centrifuge it had been taken up in an equal amount of saline according to the proper technic, but it had been placed in large jars and hand-shaken. The same shaking had been employed in each repeat washing. Toxoid "B" had been prepared in essentially the same way, but with one important difference. It had been mechanically agitated in an electrically driven churn arrangement. We believe that therein lay the explanation of the reactions produced in our Naval Academy group, i.e., inadequately washed alum-precipitated toxoid.

We have gone thus at length into the discussion of this reaction-producing toxoid to emphasize the fact that alum-precipitated tetanus toxoid, if properly manufactured, does not result in reaction on injection or reinjection, rather than to dwell upon the reactions which are here recorded, since these reactions with one exception were not serious in nature. We wish to emphasize the fact that they would not have occurred at all if the toxoid had been properly washed and prepared.

Tetanus toxoid immunization is now receiving world-wide acceptance. Tetanus toxoid immunization has been compulsory in the French army for more than five years. No case of tetanus has yet been reported in that time in any immunized individual. Tetanus toxoid immunization of the French cavalry horses has also been carried out for the last six years.<sup>8</sup> Prior to their immunization with tetanus toxoid the tetanus toxoid in these animals had been approximately 0.4 per cent over a period of six years. Thus, in 16,000 immunized horses there would have been, if unimmunized, 164 cases of tetanus. There were, in fact, none during this entire period. In more than a million persons vaccinated during military service, no serious accident was noted nor any case of tetanus. In 1937 the Italian army adopted tetanus toxoid immunization and in 1938 the English army adopted this immunization. The present war will probably yield new proof of the immunizing effect of anatoxin or toxoid.

Titration which are given in the tables which follow are taken from the U. S. Navy groups from 1934 to 1940, the largest single compilation of immunees so studied in the United States. These serum-antitoxin titration results are supported by similar results published by numerous American and European workers.<sup>9, 10, 11</sup> But more important, it is felt, in the proof of the dependability of tetanus toxoid immunization, is the experience of the large immunized groups who remain free of tetanus.<sup>12, 13</sup>

The 53 men in group I were given two injections of alum-precipitated tetanus toxoid, 0.5 cubic centimeter each, 8 weeks apart, as basic immunization. They were then given an injection of 0.5 cubic centimeter of A. P. T. T. 14 weeks later. Just before this stimulating or pick-up injection, blood was drawn for antitoxin titration (titration A), and 1 week afterward another titration was made (titration B).

The 77 men in group II were given two injections of alum-precipitated tetanus toxoid, 0.5 cubic centimeter each, 8 weeks apart, as basic immunization. They were then given an injection of 1.0 cubic centimeter of A. P.

## Tetanus in Modern Wars

Military Force	Date	Incidence per 1000 wounded	Mortality (per cent)
British Legion in Spain.....	1833-40	12.5	88.2
British in Turkey and Crimea.....	1854-56	1.5	82.1
Italian War with Austria.....	1859-61	10.0	92.4
American Civil War.....	1860-65	2.0	89.3
German in Franco-Prussian War.....	1870-71	3.5	90.0
British Expeditionary Force in France and Belgium.....	1914	5.2	—
British Expeditionary Force.....Total.....	1915-19	1.5	50.0
German-all fronts.....	1914	3.8	75.0
United States in France and United States of America.....	1917-18	0.2	11.1

Prior to the World War, in those who contracted tetanus, the mortality rate was close to 90 per cent. In the German army, during 1914, when troop movements were rapid and lines not stabilized, the incidence was high and the mortality reminiscent of the Franco-Prussian War. When lines were stabilized, and medical service prompt and efficient, the incidence of tetanus dropped to 0.8 per thousand in the German forces, and 0.2 per thousand in the United States troops, with case mortality in the United States cases as low as 11.1 per cent.

"In view of the results to be anticipated from active immunization against tetanus—namely, that the general use of this method would definitely prevent almost every case of tetanus—even the low rates for tetanus prevailing in the closing years of the World War are far too high.

"Neither the location nor type of our future operations is known. Wherever they may be, delay in antitoxin administration would certainly cause increased tetanus. Such delay is favored by the speed and range of our air and surface craft, the use of small groups of men in landing forces, and by the trends in aviation and in ground mechanization of troops,—all of which are factors tending toward wide range of action and consequent remoteness from base medical attention."

The case for tetanus toxoid immunization has been ably and very completely presented by many writers.<sup>16, 17, 18</sup> The uniformity of satisfactory immunization, the freedom from untoward reactions, and the thermostability of alum-precipitated tetanus toxoid have all been well documented. In this discussion, designed particularly to recount our experiences with toxoid immunization in the United States Navy, further repetition or amplification of these points is not necessary.

Likewise, it is unnecessary to dilate upon the disadvantages of the use of antitoxin. We all recognize the fact that when properly and promptly used antitoxin prevents all but a few cases of tetanus and that only those which develop unrecognized die in spite of antitoxin. It is well known that antitoxin, when injected prophylactically, protects only for a relatively short time and that the steadily falling curve of antitoxin in the blood reaches zero in about two weeks after an injection. We also recognize the dangers

TABLE IX  
Group III.—*Antitoxin titrations* (U. S. S. *Relief*)  
[Units per cubic centimeter of serum]

Volunteers no.	A	B	C	D	E*	F	G	H
12-III.....	0	0.0004	0.040			0.01	0.10- 0.250	3-5.0
44-III.....	0	.005	.010- 0.10			.010- .04	.01- .040	5.0
45-III.....	0	.001	.01	0.01	0.01			
47-III.....	0	.020	.010- .04					
48-III.....	±	.002	.01	.04				
49-III.....	0	.005	.100- .25	.01-.10				
50-III.....	0	.005	.010		.04			
53-III.....	±		.010- .10		.040- .10			
54-III.....	0	.001	.010	.010- .10	.010- .04	.010- .04	.02	3.0
55-III.....	±	.002	.040	.010- .02	.040- .10			
56-III.....	0		.010	.010	.01- .04			
101-III.....	0	.001	.010	.020	.010- .04			
Average....	±	.004	.035	.030	*.053	.050	.070	4.0

Three doses of old toxoid; 6-week interval between first and second injections and 2-week interval between second and third injections were given in basic course.

*Titration.*—A, 6 weeks after first dose (just before second was given); B, 2 weeks after second dose (just before third was given); C, 6 weeks after third dose; D, four months after third dose; E\*, 10 months after third dose; F, 17 months after first dose and just before an injection of 1 cubic centimeter of alum-precipitated toxoid; G, 2 days after the dose of A.P.T.; H, 7 days after the dose of A.P.T.

\* The titration giving the highest average response to the basic immunization is indicated by an asterisk (\*).

TABLE X  
Group IV.—*Antitoxin titrations* (U. S. S. *Relief*)  
[Units per cubic centimeter of serum]

Volunteers no.	A	B	C*	D	E	F	G
16-IV.....	0	0.00040		0.010	0.010	0.040- 0.10	3-5.0
46-IV.....	±	.00100	0.010- 0.04	.010- .04	.010	.010	.25- .5
Average.....	±	.00070	.025	.017	.010	.040	2.180

Three doses of old toxoid with 2-week intervals between first and second doses, and between second and third doses, were given in basic course.

*Titration.*—A, 2 weeks after first dose; B, 2 weeks after second dose; C, 2 weeks after third dose; D, 10 months after third dose; E, 17 months after first and 16 months after third dose, and just before an injection of A.P.T.; F, 2 days after dose of A.P.T.; G, 7 days after dose of A.P.T.

\* The titration giving the highest average response to the basic immunization is indicated by an asterisk (\*).

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TABLE XIII  
Group II—77 subjects (Naval Academy, 1938)  
[Units of antitoxin per c.c. of blood serum]

No.	Titration A	Titration B	No.	Titration A	Titration B
II-54.....	0.025	0.25	II-94...	.01	.5
II-55.....	.075	1.0	II-95.....	.025	.25
II-56.....	.05	.25	II-96.....	.1	>1.0 - <1.5
II-57.....	>.05 - <.075	.75	II-97.....	.05	.1
II-58.....	.05	.75	II-98.....	>.05 - <.075	.5
II-59.....	>.05 - <.075	.5	II-99.....	.025	.5
II-60.....	.05	.75	II-100....	.075	.75
II-61.....	.025	>.75 - <1.0	II-101....	>.1 - <.15	.25
II-62.....	.05	.5	II-102....	.05	.5
II-63.....	.05	.25	II-103....	.1	>2.0 - <2.5
II-64.....	.025	1.0	II-104....	<.01	.1
II-65.....	.05	.5	II-105....	>.1 - <.15	1.0
II-66.....	>.075- <.1	1.0	II-106....	.05	1.0
II-67.....	.025	.25	II-107....	.05	.5
II-68.....	>.1 - <.15	>2.0 - <2.5	II-108....	.075	1.0
II-69.....	>.1 - <.15	>1.0 - <1.5	II-109....	.05	.25
II-70.....	<.01	.1	II-110....	.1	.25
II-71.....	>.025- <.05	.25	II-111....	.05	.1
II-72.....	>.1 - <.15	1.0	II-112....	.01	.25
II-73.....	>.025- <.05	1.5	II-113....	>.025- <.05	>.25 - <.5
II-74.....	.1	1.0	II-114....	>.05 - <.075	1.0
II-75.....	.01	.25	II-115....	.1	.5
II-76.....	.01	.25	II-116....	.1	1.0
II-77.....	.025	.5	II-117....	.075	.25
II-78.....	>.05 - <.075	>2.0 - <2.5	II-118....	.075	.75
II-79.....	>.01 - <.025	.1	II-119....	.05	.25
II-80.....	.075	.5	II-120....	.025	.75
II-81.....	.01	.5	II-121....	.05	.75
II-82.....	.025	>1.0 - <1.5	II-122....	.025	>.075- <.1
II-83.....	>.025- <.05	>.075- <.1	II-123....	>.1 - <.15	1.0
II-84.....	.1	>2.0 - <2.5	II-124....	.01	.25
II-85.....	>.1 - <.15	>2.0 - <2.5	II-125....	.05	.75
II-86.....	.05	1.5	II-126....	.025	.25
II-87.....	.075	>2.0 - <2.5	II-127....	.05	>.25 - <.5
II-88.....	.025	.25	II-128....	.025	.5
II-89.....	.05	.75	II-129....	.1	1.0
II-90.....	.025	1.0	II-130....	.01	.25
II-91.....	.1	1.5			
II-92.....	.1	.5			
II-93.....	.025	.1			
			Average	.055	.684

T. T. 19 weeks later. Just before this stimulating or pick-up injection, blood was drawn for antitoxin titration (titration A), and 1 week afterward another titration was made (titration B).

What is the minimum antitoxin level necessary for protection against tetanus? Many attempts have been made to determine this level in animals. Gold<sup>14</sup> arbitrarily chose a level of 0.1 unit per c.c. as the level necessary for protection. We<sup>1, 2</sup> have shown in repeated cases that individuals with a serum-antitoxin level of only 0.01 unit per c.c. of serum respond rapidly with high blood antitoxin levels upon toxoid stimulation. Toxin will naturally produce the same stimulation. The antigenicity of toxoid and toxin are the same. The toxicity only has been changed by formolization. Tetanus infection would thus produce the same stimulus necessary to anti-

of ward and clinic patients on whom routine studies were made. An attempt has been made to correlate the findings with the patient's history.

Of the two hundred patients we examined there were 133 males and 67 females; the youngest was 15, the oldest 75, and the average age 37 years. In each of 128 patients a definite lesion was seen in the stomach and the following diagnoses were made; gastritis in 51, cancer in 42, peptic ulcer in 29, and benign polyp in 6. In 72 patients no stomach lesion was found.

*Cancer.* Schindler and Templeton<sup>1</sup> state that in the case of neoplasm of the stomach the roentgen-ray and gastroscopic diagnoses usually agree. Schloss, Ettinger and Pratt<sup>2</sup> also hold this opinion and Schatzki<sup>3</sup> believes that gastroscopy is a definite adjunct in diagnosing cancer of the stomach where the roentgen-ray diagnosis is uncertain or incorrect. Our findings agree with these opinions.

Of the 42 patients having cancer 70 per cent were male and 30 per cent female. Sixty-eight per cent gave a history of gnawing pain in the epigastrium occurring between meals, anorexia, inability to take solid food, and loss of weight. The gastric analysis in 66 per cent of these patients showed a low total and no free hydrochloric acid, and there was occult blood in all specimens.

The gastroscopic and roentgen-ray diagnosis was the same or similar in 71 per cent of the patients having cancer. In 62 per cent the diagnosis was confirmed by a microscopic study of sections secured at operation or necropsy. In three instances in which there was negative roentgen-ray evidence the lesion was diagnosed by gastroscopy and in five with negative gastroscopic evidence the diagnosis was made by roentgen-ray. The gastroscopic examination was unsatisfactory in four of these patients due to lack of co-operation.

*Peptic Ulcer.* A peptic ulcer was found in each of 29 patients, twenty-eight male and one female. The youngest patient in this group was 20, the oldest 65, and the average age 40 years. The symptoms in 58 per cent of these patients included epigastric pain occurring one to two hours after meals, and at night, sour eructations, nausea and vomiting. Usually relief from these symptoms was obtained after taking alkalies. Fractional gastric analysis showed hyperacidity in 33 per cent of these patients, with occult blood in all specimens.

Regarding the respective merits of the methods of diagnosing gastric ulcer Schatzki<sup>3</sup> concludes that large ulcers are more easily diagnosed by roentgen-ray, whereas small ulcers may be missed on roentgen-ray examination but can usually be seen gastroscopically; while Schloss, Ettinger and Pratt<sup>2</sup> feel that ulcers are more frequently discovered by gastroscopy than by roentgen-ray. Palmer, Templeton and Schindler<sup>4</sup> studied a series of 50 patients having gastric ulcer with careful roentgen-ray compression technic and gastroscopy and their comparative findings showed that the diagnoses were identical by both methods in 32 patients, and that they were made by

It is surely not necessary to recommend tetanus toxoid immunization by citing the accidents which occur in the use of antitoxin: i.e., serum sickness, anaphylaxis, and the like. Yet it may be noted that many of the cases which have been referred to us for tetanus toxoid immunization have been those who have experienced the most severe reactions when taking antitoxic serum, and yet experienced no untoward reaction upon injection of toxoid. The group of allergic patients, asthmatics and hay fever sufferers, should also be an important one for the use of toxoid in civilian life.

The combination of tetanus toxoid with diphtheria toxoid, which is highly successful in the immunization of children, is not desirable for use in the Navy. Diphtheria is not a problem in adults; and it is well to avoid the reactions incident to the use of diphtheria toxoid in adults.

It is felt that the introduction of toxin by other routes, such as nasal drops, is not sufficiently positive to be relied upon, even though it has been demonstrated that antitoxin does rise after application of toxoid to the nasal mucosa.<sup>14</sup> A subcutaneous or intramuscular injection is slightly if any more uncomfortable than a nasal swabbing.

In the light of available data, the present minimum protective plan which we in the Navy contemplate is obviously far more comprehensive than is necessary. At present, it seems wise to over- rather than under-immunize. Later, in the use of tetanus toxoid immunization, it may be determined how close one can run to the lower margin of safety. Our plan is that after the basic immunization with two injections of alum-precipitated tetanus toxoid eight weeks apart, a man, when wounded, receives an injection of toxoid; and all cases regardless of injury, once having been immunized, receive an injection of toxoid every four years thereafter. Doses subsequent to the first injection act as a stimulating or booster dose, raising both the humoral and tissue immunity. Illustrations of this fact can be found in all our tables, particularly in table 4, in which a few of the men who were immunized in 1934-36 were titrated before, and a week after, a dose of toxoid given in January 1940.

It may be of interest here, to quote a section from "Tetanus in War Time."<sup>2</sup>

"The importance of tetanus in civil life may be small. In warfare, however, the conditions which minimize the importance of tetanus in civil populations are completely reversed, and high incidence of tetanus, with its great mortality rate, becomes a major medical problem. In civil life wounds are few, often superficial and uncontaminated, and antitoxin is quickly available. War wounds, on the other hand, are notably deep, with much devitalized tissue and soil contamination, and serum is often not promptly available.

"The accompanying table shows the important rôle tetanus has played in modern wars.

"It will be noted that the incidence of tetanus has varied considerably according to the type of war and the soil pollution in the theater of war.



hyperacidity, 32 per cent with hypoacidity, 21 per cent with anacidity and 15 per cent refractory to histamine. Boros<sup>7</sup> states that gastric analysis is not an index to inflammation of the stomach.

*Polypi.* A benign polyp of the stomach was diagnosed by gastroscopy in six patients, of which four were male and two female. The youngest was 15, the oldest 56, and the average age 53 years. On one of these patients no roentgen-ray was made, polyp was suspected in two, cancer in two others, and in one patient the stomach was considered negative. However, subsequent operation and histological section proved both cases in which cancer was suspected to be benign polyp.

The superiority of gastroscopy in diagnosing benign tumors of the stomach, as shown in this group of patients, has been reported by Schindler, Gutzeit and Teitge on many occasions.

The symptoms of which these patients complained included epigastric pain, nausea, vomiting, anorexia, diarrhea and loss of weight. However, there was no one symptom common to all patients. A gastric analysis was performed on two of these patients. In both instances occult blood was present. The curve was normal in one case and showed no free hydrochloric acid in the other.

#### SUMMARY

Of the 200 patients examined by both roentgen-ray and the gastroscope a lesion of the stomach was found in 128 cases. If we include the patients having gastritis we find that the roentgenological and gastroscopic diagnoses were the same in 62 per cent of all the cases. However, since the diagnosis of gastritis was not made in a single instance by roentgen-ray it might be a truer comparison of the value of the two methods of examination in identifying organic disease to omit these cases. When this is done the same diagnoses have been made by gastroscopic and roentgen-ray examination in 87 per cent of all the cases. The diagnoses of lesions of the stomach were made by roentgen-ray in 10 cases where the gastroscopic evidence was negative, whereas the diagnosis was made by gastroscopy in 15 patients when the roentgen-ray evidence was negative.

Of the 42 cases of gastric cancer 34 were diagnosed by both methods, 5 by roentgen-ray and not by gastroscopy and 3 by gastroscopy and not by roentgen-ray.

Of the 29 patients having gastric ulcer 18 were diagnosed by both methods, 5 by roentgen-ray and not by gastroscopy and 6 by gastroscopy and not by roentgen-ray.

Of the 6 patients having polyps of the stomach one was diagnosed by both methods, 5 by gastroscopy alone and none by roentgen-ray alone.

Total Patients Examined .....	200
Total Patients with Gastric Lesion .....	128
Total Patients without Gastric Lesion .....	72

and discomforts of serum sickness and allergy. In spite of these shortcomings and disadvantages, tetanus antitoxin will probably never be entirely discarded. There will always be a large number of individuals who are not immunized: millions of patients and many doctors who operate by hindsight rather than foresight. Nevertheless, tetanus toxoid immunization is so completely fitted to our needs in the military services, and to all other groups which can be well controlled medically, that its universal adoption, under such control, seems inevitable.

### SUMMARY

1. Immunization with tetanus toxoid has been studied in the U. S. Navy since 1934. Volunteer groups were used at first.

2. Active immunization against tetanus, by means of plain or alum-precipitated tetanus toxoid, is a safe and reliable procedure.

3. With properly prepared toxoid, reactions are minor and infrequent. We report some reactions encountered when using a certain toxoid, the reactions probably being caused by inadequate washing of the alum-precipitated toxoid during preparation.

4. Toxoid immunization has now been adopted by the French, Italian and British armies.

5. No case of tetanus in a toxoid immunized individual has yet been reported.

6. The actual antitoxin level in the blood is not of prime importance. Basic immunity, or ability of tissue to react with the production of antitoxin, is the essential condition.

7. The present plan, in use in the Navy, is two injections eight weeks apart as basic immunization; injection at the time of injury if deemed necessary to raise blood antitoxin rapidly; injection each four years after basic immunization to maintain immunity at a high level.

8. All midshipmen at the U. S. Naval Academy are now routinely immunized with alum-precipitated tetanus toxoid. More than 3400 have been so protected, as well as many other navy personnel and dependents.

9. Toxoid immunization, against tetanus, is ideally fitted to the needs of the military services and to all other groups which can be medically well controlled.

10. Its universal adoption in such groups seems inevitable.

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## VITAMINS IN PEPTIC ULCER \*

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PEPTIC ulcers have been produced experimentally in animals by deficiencies in vitamins B<sub>1</sub> and C.<sup>1,2</sup> Those were severe deficiencies and we do not have evidence that such deficiencies are usually important in the etiology of peptic ulcers in man. The possible significance of vitamins in the treatment of peptic ulcers, however, deserves serious consideration. Some conclusions, which we are to present, must be considered tentative because they are based, in part, on indirect evidence.

Vitamin C may be important in respect to the process of healing of an ulcer or in respect to its tendency to bleed. In regard to the former we do not have direct evidence. The relationship of ascorbic acid to collagen formation in experimental deficiency<sup>3</sup> and in human scurvy<sup>4</sup> and its consequent relationship to wound healing<sup>5</sup> have been well demonstrated. It might be suspected, therefore, that vitamin C nutrition may be a factor in the healing of a peptic ulcer.

Chemical evidence of suboptimal vitamin C nutrition has been found to occur with remarkable frequency. It has been particularly frequent among peptic ulcer patients. People with abdominal symptoms are apt to avoid fruits and green vegetables. Croft and Snorf<sup>6</sup> found, among their first 100 determinations of blood ascorbic acid on private patients, 38 below 0.40 mg. per cent. Of these, 15 (40 per cent) had active peptic ulcers and 13 had had recent gastrointestinal hemorrhage.

Chemical evidence of vitamin C deficiency in a large proportion of peptic ulcer patients has been reported by Harris, Abbasy and Yudkin,<sup>7</sup> Archer and Graham,<sup>8</sup> Ingalls and Warren,<sup>9</sup> Lazarus,<sup>10</sup> Portnoy and Wilkinson,<sup>11</sup> Roux,<sup>12</sup> and Rao.<sup>13</sup> These series have been small, with the exception of one, which included 56 patients, but the finding has been constant.

Our experience is in accord with these findings. Thirty-nine of 58 patients with peptic ulcer had plasma ascorbic acid values below 0.5 mg. per cent, the beginning scurvy level of Farmer and Abt.<sup>14</sup> Two of the 8 patients who had values above 0.7 mg. per cent had received supplements of synthetic ascorbic acid.

As to the relationship between vitamin C nutrition and bleeding, the findings of Croft and Snorf<sup>6</sup> have been quoted above. Portnoy and Wilkinson<sup>11</sup> reported a mean plasma ascorbic acid of 0.34 mg. per cent among 31

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## AN ANALYSIS OF 200 PATIENTS EXAMINED GASTROSCOPICALLY \*

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It has often been stated that the enthusiasm which attends the introduction of a new therapeutic or diagnostic agent is short-lived unless that agent fulfills certain requirements. In general these requirements are safety, simplicity and ease of employment, and finally, results that are dependable and of value.

It is the purpose of this paper to report on these facts as they apply to gastroscopy performed with the Wolf-Schindler flexible gastroscope in the Bronchoscopic Department of the Jefferson Hospital. It is hoped that such an analysis, added to the rather large number of studies already made, will be of value in establishing the exact status of this procedure.

The literature, both in this country and abroad, amply attests the safety of flexible tube gastroscopy. This safety is truly remarkable in comparison with the high incidence of morbidity, and even mortality, resulting from the older form of gastroscopy with the rigid instrument. Although one hears from time to time of a death attributed to this new diagnostic method there is not a single case reported in the literature to my knowledge. In a recent communication Dr. Schindler corroborated this statement, as did Moutier, Gutzeit and Henning six months ago. In our experience at the Jefferson Hospital, where flexible tube gastroscopy has been employed for over three years, no mortality has been encountered and the morbidity has been nil.

Gastroscopy with the flexible instrument is the most readily performed of all endoscopic examinations. Dr. Schindler has always insisted that it is primarily an office or clinic procedure. We have never found it necessary to hospitalize a patient for gastroscopic examination alone. Moreover, in the majority of patients the only preparation that we now employ is to have the patient present himself fasting and then have him gargle with a 2 per cent Pantocain solution. This is followed by a brief, gentle swabbing of the pharynx with the same solution on a cotton tampon. Following anesthetization the patient is placed on his left side on a table and the gastroscope passed. The average length of time for the examination is five minutes. After the examination the patient is at liberty to leave the hospital and resume whatever activity he wishes. Therefore, it is felt that the second requirement, namely simplicity and ease of employment, is adequately fulfilled.

To demonstrate the value of flexible tube gastroscopy two hundred patients have been selected in whom a fractional gastric analysis, roentgen-ray and gastroscopic examination had been performed. The group is composed

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though not proved, it is possible that such an effect on healing may be the explanation of (1) the high frequency of bleeding among those ulcer patients with plasma ascorbic acid values below 0.4 mg. per cent, (2) the infrequency of bleeding among those with higher ascorbic acid values, and (3) the occurrence of hemorrhage after considerable periods of the usual medical treatment in this hospital in two patients with plasma ascorbic acid values of 0.30 and 0.25 mg. per cent. As noted above, the bleeding in one of these was found to be from a large artery at the base of the ulcer. The relationship between vitamin C deficiency and bleeding may not remain as close in a larger series. The findings in these 58 cases, however, seem to make correction of any such deficiency indicated as part of the treatment of peptic ulcer.

Not only do ulcer patients commonly start treatment with a suboptimal vitamin C nutrition. Most ulcer diets are very deficient in that vitamin and the amounts of it required for saturation in patients receiving alkali therapy are greater than for normal individuals. Van Eckelen<sup>15</sup> and Heinemann<sup>16</sup> reported that the amount of ascorbic acid required to maintain saturation in normals was about 0.84 mg. per kilo per day (weight corrected to height). Heinemann<sup>17</sup> reported that four ulcer patients required an average of 1.25 mg. per kilo per day, and Warren, Pijoan and Emery<sup>18</sup> reported that 5 ulcer patients required an average of 1.05 mg. per kilo per day for saturation with ascorbic acid.

From 1 to 3 grams (occasionally more) of ascorbic acid are usually required to correct a significant deficiency. Two grams of ascorbic acid would be furnished by 4000 c.c. of orange juice. It seems preferable, at the beginning of ulcer treatment, to attain normal vitamin C nutrition quickly by giving moderately large doses, perhaps 200 mg., four times a day, until the plasma ascorbic acid is 0.9 mg. per cent or higher. If facilities for determination of ascorbic acid are not available and the anti-scorbutic quality of the previous diet is at all doubtful, it can do no harm to give, empirically, 2 grams of ascorbic acid in such divided doses. Thereafter, 100 c.c. of orange juice or 50 mg. of ascorbic acid may be given daily until enough other fruits and vegetables are added to the diet to make it adequate.

Other vitamins may be of importance in the treatment of peptic ulcer. We have had a few patients on an ulcer diet for a long time, taking less than the allowed amount of meat and vegetables, who have developed pellagrous symptoms. Some have had the chronic skin changes that we have described;<sup>19</sup> some have had glossitis; a few without objective evidence of pellagra have had abdominal symptoms, other than ulcer pain, relieved following the administration of nicotinic acid. Wheeler and Sebrell<sup>20</sup> reported that milk was only a fair pellagra-preventing food. Three of 5 dogs receiving 15 c.c. of evaporated milk per kilo (equivalent to 2 quarts of milk a day for a 70 kilo man) developed blacktongue.

Vitamin B<sub>1</sub>, like ascorbic acid, is easily destroyed in an alkaline medium. We have not found a significant amount of it to be destroyed when incubated with gastric juice at any physiological pH. We have found that as much

roentgen-ray only in 8 patients and by gastroscopy only in 6 patients. In four instances the patient was not gastroscoped so that the diagnosis was made entirely by roentgen-ray. Our own findings in gastric ulcer closely approximate the above.

The diagnoses made by roentgen-ray and gastroscopy were the same in 55 per cent of the patients having peptic ulcers. We considered the diagnosis confirmed in 65 per cent of the patients when they improved and were completely free of symptoms following medical management for gastric ulcer. The diagnosis was proved in four instances at operation and in one case was not confirmed.

Gastroscopic examination showed a definite gastric ulcer in each of six patients in whom the roentgen-ray examination of the stomach was negative. Each of these patients improved on ulcer therapy and was discharged from the hospital. On the other hand in five cases with positive roentgen-ray evidence of ulcer gastroscopy was negative in four and gave indefinite findings in one. Only one of these diagnoses was confirmed, and that by operation.

*Gastritis.* Fifty-one of the patients examined showed some form of gastritis. Sixty-six per cent were males and 34 per cent females. The youngest patient was 19, the oldest 68 and the average age 36 years.

The symptoms of which these patients complained most frequently were abdominal pain and loss of appetite. The pain was usually epigastric. In seven instances it occurred immediately after eating and in 24 one to two hours after eating. Belching was the next most common symptom, then fullness, nausea and vomiting. Vomiting was infrequent.

In 47 per cent of the patients with gastritis there was no apparent associated lesion of the stomach, nor of any contiguous structures. The roentgen-ray examinations in these cases revealed no abnormality of the stomach. In the remaining 53 per cent associated lesions such as cancer, gastric, stomal or duodenal ulcer, and gall-bladder disease were present. All of these lesions were seen roentgenologically but the accompanying gastritis was not diagnosed.

The majority of writers feel that gastroscopy is the best method of diagnosing gastritis and many of them agree with Gaiter and Borland<sup>5</sup> who state that it is the only means by which a definite diagnosis can be made.

In our series of cases the fractional gastric analysis showed that hyperacidity and hypoacidity occurred with about equal frequency but were found only about half as often as a normal curve. About 14 per cent of the patients in this group had no free hydrochloric acid in the stomach contents and occult blood was found in over 50 per cent of the specimens.

The great variation in the interpretation of gastric analysis findings is emphasized by the studies of Henning.<sup>6</sup> The gastric analysis curves in a series of patients reported by him, and definitely diagnosed gastroscopically as having gastritis, showed 21 per cent with a normal curve, 11 per cent with

This has not been found to be important for ulcer patients who do not continue intensive alkali therapy for long periods. Such destruction of thiamine may be the cause of combined system degeneration.

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No. Cases	Diagnosis	Made by Both Methods	Roentgen-Ray Alone	Gastroscopy Alone
42	Cancer	34	5	3
29	Ulcer	18	5	6
51	Gastritis	0	0	51
6	Polyp	1	0	5
72	Negative	71	0	1
200		124	10	66

### CONCLUSIONS

1. The histories of the majority of the patients were so similar that special examinations of the stomach were required to make a differential diagnosis.

2. Roentgen-ray and gastroscopy are the most valuable methods of examining the stomach.

3. In none of the patients were we able to make the diagnosis by the gastric analysis alone. However, in a certain proportion of instances this examination was of significant help.

4. Gastroscopy has been shown to be a safe diagnostic procedure.

5. Gastroscopy can be employed simply and easily.

6. The value of gastroscopy is demonstrated by the fact that it is the most definite method whereby the diagnosis of gastritis and benign tumors can be made. Furthermore, in cases of ulcer or malignancy of the stomach gastroscopy is a definite adjunct to roentgen-ray examination.

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There are 235 instances of multiple familial occurrence. Conner<sup>6</sup> cited 110 in 1931; 105 have been found in the literature since then; and I have added 20 more families, in 18 of which the proof is definite (tables 1 and 2).

TABLE I  
Families in Which Two or More Members Have Pernicious Anemia

Authors	Number of Families	Relatives Involved			
		Siblings	Two Direct Generations	Patient and Aunt or Uncle	More Distant or not Stated
62 * Personally collected	215	41	48	4	122
	20	9	9	2	—
Total	235	50	57	6	122

\* Bibliography, 6 to 32 inclusive.

The data in many individual families supply convincing evidence as to the hereditary pattern. Consanguineous marriages are of particular value in that they should make recessive traits manifest (chart 1).

5 CASES OF PERNICIOUS ANEMIA IN  
13 CHILDREN IN ONE GENERATION.

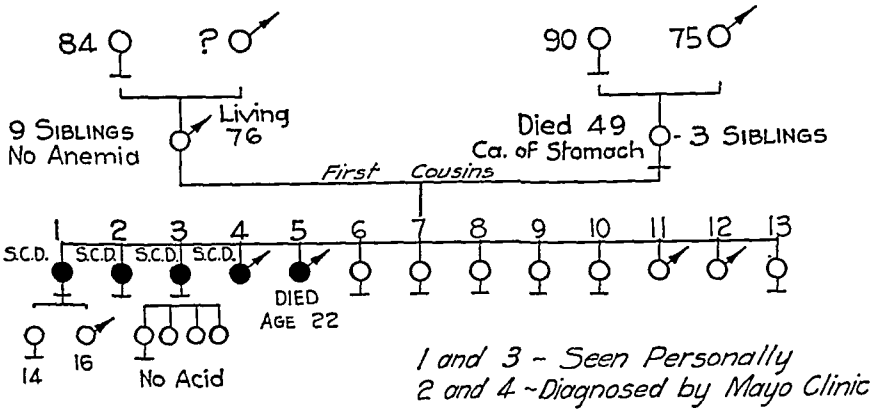


CHART I

Family J of our group is interesting. Two first cousins, whose parents lived to old age, married and had 13 children, of whom five had pernicious anemia (four proved). Two of these children, sisters, I personally have observed, both of whom showed a macrocytic hyperchromic anemia, an-acidity after histamine and subjective and objective signs of spinal cord degeneration. Another sister died at the Mayo Clinic on October 19, 1917, diagnosed as pernicious anemia. A brother was seen at the Mayo Clinic

TABLE I  
Plasma Ascorbic Acid in Peptic Ulcer Patients †

Plasma Ascorbic Acid—Mg. %	Number of Patients	Patients with Hemorrhage
0.20-0.29	10	3
0.30-0.39	15	7
0.40-0.49	14	1
0.50-0.59	8	0
0.60-0.69	3	0
0.7 -more	8*	1
Total Cases	58	12

\* Two of these patients had received supplements of ascorbic acid.

† We are indebted for some of these analyses to Dr. J. G. Ruth and Dr. W. D. Block.

patients admitted for hemorrhage, contrasted with a mean plasma ascorbic acid of 0.42 mg. per cent among 25 patients with proved ulcers, without hemorrhage. Twelve of our 58 patients were bleeding at the time of admission, or while in the hospital. This incidence is about four times that of bleeding among other ulcer patients in this hospital during the same period. This was not a consecutive series, but the fact that ulcer patients with hemorrhage were more apt to have determinations of their plasma ascorbic acid done, adds to the significance of the figures. Ten of the 12 that bled were among the 25 who had plasma ascorbic acid values below 0.40 mg. per cent. It is probably of significance that two patients in this group had their hemorrhages after they had been in the hospital on an ulcer regime for 18 and 26 days respectively. Their plasma ascorbic acid values were 0.30 and 0.25 mg. per cent, respectively. One of these patients was found at autopsy to have an erosion into a large artery. One wonders if the treatment in these two cases would have been more effective if the deficiency in ascorbic acid had been remedied.

Two patients who were included in this group because of hematemesis despite negative roentgen-ray findings after the bleeding had ceased probably do not belong here. They had clinical scurvy evidenced by gingivitis and subcutaneous bleeding. One had subcutaneous bleeding only on capillary fragility test. The other lacked gingivitis but had spontaneous subcutaneous bleeding. Another patient with hematemesis and melena was not included because no ulcer could be demonstrated at autopsy. He did have subserosal and other hemorrhages and the plasma ascorbic acid of his heart's blood was 0.34 mg. per cent. He was edentulous and had no subcutaneous bleeding. It seems probable that in a certain proportion of cases, gastrointestinal hemorrhage, for which no cause can be found when roentgen-ray examination is feasible, is due to scurvy rather than to acute peptic ulcer.

Other than a scorbutic type of bleeding, hemorrhage from a peptic ulcer may be regarded as the result of an unfavorable balance between erosion and reparative processes. If a vitamin C deficiency impairs the healing process it might be expected to promote the occurrence of bleeding. Al-

TABLE III  
Pernicious Anemia in Twins

Author	No.	Uniovular	Sex	Age
Frank.....	1	Yes	M.	57—Both developed pernicious anemia within 1½ years. Both had Towerskulls, both developed paralysis agitans, both high grade morons (mental age 8).
Ellis (Cited by Hurst) ..	2	Yes		Both proved (details unobtainable).
Bremer (Cited by Weitz)	3	Not stated (probable)	F.	Both proved (details unobtainable).
Kaufmann and Thiessen	4	Yes	F.	55—Developed pernicious anemia within 8 years. One first to develop it always in poorer health. Both diabetics.
	5	Yes	F.	68—One pernicious anemia. Other normal blood smear but no blood count done, no gastric analysis. Had hypersegmentation of leukocytes.
Werner.....	6	Yes	M.	57—One pernicious anemia. Other—"anacidity." Since brother developed pernicious anemia has eaten liver, preventing later recognition.
Strandell.....	7	Yes	F.	68—Died with cord involvement. Other "achylia," numbness in one foot, no anemia. Considered incipient anemia.
Dedichen.....	8	"Resembled each other"	F.	86—One "pernicious-like anemia" with "achylia" test not stated. Other had "pernicious-like anemia" with free acid.

disease has appeared in both members; in three, it is probably latent in the second member. In one pair, aged 86, although there is anemia in both, the second member has free acid present. The data in this last instance are so meagre that the diagnosis can well be questioned in both twins.

This is strong evidence for heredity as an etiological factor in these instances, but control studies of dizygotic twins should be made.

#### ANACIDITY IN RELATIVES

Increased frequency of pernicious anemia among relatives should be reflected in an increased incidence of its precursor, anacidity.

All the studies of relatives analyzed as to age and the nearness of blood relationship show an increased incidence of anacidity, particularly in the two decades prior to 40, and about a double percentage of anacidity among the near relatives as opposed to distant relatives (tables 4, 5, 6, 7).<sup>27, 33, 6</sup>

#### ANACIDITY PRECEDING PERNICIOUS ANEMIA

Test meal anacidity has been found to precede pernicious anemia for from 2 to 30 years in 57 of 60 patients (table 8).<sup>20, 35</sup> These 60 cases were obtained by selecting from a group of 1061 patients previously studied those with previous gastric analyses.

Individual case reports of anacidity preceding pernicious anemia by many years have been collected. It has been found that of a total of 174 cases in

as 56 per cent of thiamine, incubated with bile or pancreatic juice at their natural pH may be destroyed.<sup>21</sup> Also, there is a considerable adsorption of thiamine when it is exposed *in vitro*, to some anti-acids in gastric juice. We have not determined exactly how much of the absorbed thiamine may be recovered by the body but judge from our findings that a major portion of it is recovered.

The Sippy regime, with its hourly milk and cream, contains a good amount of thiamine. Nevertheless, we have found that, during the third week on that regime, 19 of 20 patients had a urinary excretion of thiamine in the range of patients with a definitely deficient intake.<sup>22</sup> Eleven of 17, however, excreted a normal fraction of a 5 mg. test dose of thiamine given with a meal. The low excretion before, and the normal excretion after the test dose are findings obtained after a short period of experimental thiamine deficiency, indicating that the body stores of the vitamin are not seriously depleted. Thiamine deficiency, as well as alkalosis, may be a cause of anorexia in ulcer patients receiving intensive alkali therapy, and might become of greater importance if such treatment were continued over a long period. We have not found positive chemical evidence of thiamine deficiency in patients on six meal ulcer diets with less than hourly doses of alkalis.

The destruction of thiamine in bile and pancreatic juice, the alkalinity of which is unmodified by stomach acid, is possibly of more significance in another situation. Patients with achlorhydria require a larger intake of thiamine than do subjects with a normal gastric acidity. Consequently, as we have found,<sup>22</sup> they are apt to show chemical evidence of thiamine deficiency. It is suggested that this may be an explanation of the cord changes in pernicious anemia.

#### SUMMARY AND CONCLUSIONS

The majority of patients with peptic ulcer studied have a deficiency in vitamin C.

The pathology of vitamin C deficiency is such that it might be suspected to have a deleterious effect on the healing of a peptic ulcer.

The correlation between low plasma ascorbic acid and the occurrence of hemorrhage in peptic ulcer is suggestive evidence of such an impairment of healing.

Some patients considered to have had an acute peptic ulcer, and with negative roentgen-ray findings after bleeding had ceased, probably had a scorbutic bleeding.

It seems indicated, in the treatment of peptic ulcer, to correct promptly any vitamin C deficiency.

Ulcer patients may develop a pellagrous type of deficiency if they continue to restrict meat and green vegetables.

Ulcer patients receiving intensive alkali therapy show chemical evidence of a deficiency in vitamin B<sub>1</sub>. A large proportion of thiamine incubated with bile and pancreatic juice at their natural pH is destroyed *in vitro*.

TABLE VII  
Percentage of Incidence of Anacidity in Relatives in Various Decades of Life  
(Histamine)

Age (Years)	No. of Subjects	No. with Anacidity	Per Cent Anacidity	Per Cent Anacidity 654 Normals (Pollard)
0-20	5	1	20	0
20-29	14	1	7.1	3.5
30-39	22	5	22.7	5.2
40-49	12	1	8.3	14.3
50 plus	8	2	25	20.6
	61	10	16.3	12

This shows an increased incidence prior to 40. This may be due to those with the early developed anacidity of potential pernicious anemia. Only analysis of a large group of histamine anacid relatives can determine if the increased incidence of anacidity in all ages is due to increased incidence before 40.

TABLE VIII  
Achlorhydria Preceding Pernicious Anemia  
(Test Meals)  
Representing study of group including all preceding gastric analyses.

Group	No. with Preceding Gastric Analyses	No. with Anacidity
Strandell.....	117	20
Rozendaal.....	906	34
Personal cases.....	38	3
Totals.....	1061	57

which previous gastric analyses had been recorded 171 had shown anacidity (table 9).

TABLE IX  
Achlorhydria Preceding Pernicious Anemia, Including All Reported Cases (Test Meals)

	No. of Group Studied	No. with Preceding Gastric Analyses	No. with Anacidity	No. of Authors
Ivy, Morgan and Farrell*.....	?	34	34	20
Murphy, W. P.....	(1)			
Schemm, F. R.....	(2)	3	3	2
Meulengracht.....	368	77	77	1
Strandell.....	117	21	20	1
Rozendaal.....	906	36	34	1
Askey.....	38	3	3	1
Totals.....		174	171	26

\* Their 36 reported cases include two by Conner, which are probably duplicated by Rozendaal.

# PREVENTION OF PERNICIOUS ANEMIA: RECOGNITION OF THE LATENT STAGE IN RELATIVES\*

By JOHN MARTIN ASKEY, F.A.C.P., *Los Angeles, California*

THE diagnosis of Addisonian pernicious anemia ordinarily is made over a year after symptoms have been definitely established.<sup>1</sup> About 75 per cent of patients with this disease have involvement of the nervous system,<sup>2, 3</sup> and this condition is often recognized too late to prevent partially disabling nervous system lesions. The deaths attributable to pernicious anemia are due largely to complications of these lesions. Treatment may prevent further progress but cannot correct irreparable spinal cord damage.

The challenge for the future must be to diagnose pernicious anemia before the appearance of blood and nervous system changes. This will inaugurate an era of prophylaxis in pernicious anemia.

We wish to review the accumulating evidence that the potential cases of the disease are in the relatives and to suggest a scheme by which they may be recognized in the latent stage.

## HEREDITY AND PERNICIOUS ANEMIA

Hereditary predisposition is becoming more and more generally accepted although it often is difficult to prove in an isolated instance. To establish heredity as an etiological factor in a human disease such as Addisonian pernicious anemia, which is relatively rare and tends to appear late in life, is difficult.<sup>4, 5</sup>

Where accurate family histories are impossible to obtain for several generations the pedigree method is unreliable. The number of living parents available for study is small. The determination of an increased frequency of consanguineous marriages in parents, which would suggest a recessive type of inheritance, is difficult. The demonstration that the disease occurs more frequently in two members of a family than can be accounted for by chance alone is, however, good statistical evidence.

The most conclusive data are those obtainable from the study of twins. Hereditary diseases must show an invariable occurrence in both uniovular twins, if one has the disease.

## FAMILY INCIDENCE

Despite the difficulties incident to the pedigree method, pernicious anemia has been found in several members of families to an extent far above the expectation from chance alone. The grouping in certain families is so marked that the genetic factor cannot be questioned.

\* Read at the Cleveland meeting of the American College of Physicians April 2, 1940.  
From the Department of Medicine, University of Southern California School of Medicine.

## STUDY OF FAMILIES

To discover *latent* pernicious anemia, we have considered every relative as a potential case until disproved. We have told every patient of the familial nature of the disease, and have requested each to have his relatives come in for a histamine gastric analysis. Many relatives refused, but 61 agreed to this study, of whom 10 showed anacidity. The 51 with acid were arbitrarily considered as in no imminent danger, and the 10 with anacidity were considered as potential cases who, in later years, might develop the disease. The assumption of anacidity based on a single histamine study we realize is again arbitrary, but is necessary due to the difficulty of getting even a single test in normal relatives.

To avoid any phobia which might lead to premature eating of liver and the prevention of early recognition, they were not told the early symptoms.

In the families thus studied the following developments have occurred: Two relatives who refused gastric analyses have developed severe crippling pernicious anemia. Of the 10 anacid relatives, four have developed signs or symptoms of early pernicious anemia; two have developed hypochromic anemia, apparently idiopathic. Three have normal blood, and one cannot be located.

## PREVENTION OF PERNICIOUS ANEMIA

The following cases we believe are significant:

I. Two individuals, because of pernicious anemia in the family, were considered possible potential cases of the disease. They were both in good health and refused gastric analysis. In two and five years respectively they developed pernicious anemia with marked spinal cord damage. Despite treatment one is totally disabled and one is partially disabled.

It is highly probable that if they had allowed gastric analyses, true anacidity would have been found, and they would have been watched for early symptoms.

## CASE REPORTS

*Family 1.* Mrs. M.D., aged 69 years, has been under treatment for pernicious anemia since June, 1935. A gastric analysis on her daughter done in 1936 showed hypoacidity. The son, aged 48 years, was in good health in 1936 and refused a gastric analysis. In May, 1938, Dr. Robert W. Langley saw him with an attack of severe precordial pain. The electrocardiogram failed to show coronary occlusion. The blood count showed 1.7 million erythrocytes, 40 per cent hemoglobin (Sahli), and a typical blood smear of pernicious anemia. There were diminished patellar reflexes, dysmetria in the heel to knee test, diminished vibratory sense and impaired sense of position. There was marked instability in walking. There was no free hydrochloric acid after histamine stimulation. His response to liver therapy given parenterally was typical. In March, 1939, his erythrocytes were 4.3 million and his hemoglobin (Sahli) 80 per cent. He is now totally disabled. Although able to walk without a cane, he is ataxic and mentally "has lost his grip." Formerly a high business executive, he now can transact little business.

on October 14, 1936, and diagnosed pernicious anemia, with subacute combined cord degeneration. The other brother, by hearsay, was said to have died at the age of 22 of pernicious anemia.

TABLE II  
Pernicious Anemia in Several Members of a Family  
(Since Conner, 1930)

Families		Relationship
Moschcowitz, F.....	1	"Five members in three generations."
Hartfall and Witts.....	1	Patient, sister and two maternal aunts.
Ridder.....	1	Patient, sister, and maternal aunt.
Liepelt.....	1	Mother and daughter.
Frank.....	1	Identical twins.
Winternitz.....	2	(1) Three brothers. (2) Father and son.
Ungley and Suzman.....	1	Brother and sister.
Dobriner and Rhoads.....	1	Father and son.
Wilkinson and Brockbank.....	14	(1) 4 siblings. (2) 9 times in two or more generations. (3) Once—patient and aunt.
Piney.....	1	Patient and father.
Krantz.....	1	Patient and mother.
Beebe and Wintrobe.....	1	Patient and mother.
Ellis (Quoted by Hurst).....	1	Identical twins.
Strandell.....	3	(1) Mother and son. (2) Brother and sister. (3) Identical twin sisters.
Heath.....	1	Two sisters and brother.
Scheidel (Cited by Ridder).....	1	Patient and sister.
Horsters and Krohn (Cited by Ridder).....	2	"Two families."
McGhie.....	1	Daughter, father and mother.
Finney.....	1	"Patient and relative."
Murphy.....	40	"Two or more members."
Kaufmann and Thiessen.....	8	(1) 4 siblings. (2) Mother and son (twice). (3) Cousins. (4) Identical twins.
Schemm.....	6	(1) 5 siblings. (2) Mother and son.
Weitz.....	10	"Through three generations."
Bremer (Cited by Weitz).....	1	7 cases in three generations, including two femi- nine twins.
Naegeli.....	3	(1) Mother and daughter. (2) Four relatives. (3) Father and son.
Michaud (Cited by Askanazy).....	1	Father and son.
Askey *.....	20	(1) 9 siblings. (2) 9 in two generations. (3) Patient and uncle. Patient and nephew.
Total.....	125	

\* I wish to thank members of the Section of Internal Medicine of the Los Angeles County Medical Association for permission to report 10 of these families.

Since this paper was written, I have discovered another family, daughter aged 43, and mother aged 82, with definite cord damage in both; also another report of a boy, 18, and his mother, 48, with pernicious anemia, by Wilkinson, J. N., *in* Clin. Va. Mason Hosp., 1939, xviii, 19.

#### STUDY OF IDENTICAL TWINS

Studies of identical twins, one of whom had pernicious anemia, have been reported in eight pairs (table 3).<sup>11, 19, 30, 27, 33, 20, 34</sup> In four pairs the



III. Two other anacid relatives, aged 64 and 62, show slight anemia, but the most significant changes are those of macrocytosis in the blood smear, confirmed by definite increased mean cell volume, and color and volume indexes over one (table 10).

Davies and Illyd-James<sup>40</sup> found only one in 14 normal people over the age of 60, with true anacidity, with a color index over one. In adults, age has no effect on the size of the red blood cells. Both of these relatives are in poor health, one with slight impairment of vibratory sensation and a smooth tongue.

IV. Two anacid relatives apparently have developed an idiopathic hypochromic anemia. It has not been proved that there is not latent or coexistent pernicious anemia.

#### CASE REPORTS

*Case 1.* Mrs. R. G., aged 43, showed true anacidity after histamine January 28, 1935. Her mother was under treatment for pernicious anemia with marked cord involvement. She was in good health and consented to a stomach analysis only after considerable persuasion. A blood count then recorded showed hemoglobin 12.9 grams, erythrocytes 4.10 million (color index 1.09), leukocytes 6,555, with slight variation in size and shape of the red cells. She moved away from town soon afterward and for several years attempts to locate her failed. March 1, 1940, she was located in a distant town and gave the following history: About 1937 she developed some tingling in her hands and some transient soreness of her tongue. Remembering that her mother had had similar symptoms and that I had emphasized the familial nature of the disease, she took various liver and iron preparations which her husband, a druggist, suggested. She still lost weight and developed severe headaches.

In February, 1939, her blood count showed erythrocytes 3.68 million, and hemoglobin (Newcomer) 71 per cent.\* From February to May, 1939, she took oral liver but in May the hemoglobin was 59 per cent and the erythrocytes 3.8 million. She was then given large doses of iron supplemented by copper.

On February 16, 1940, her hemoglobin was 83 per cent and erythrocytes 3.97 million. She has gained eight pounds and her headaches are better. There was at no time any reason to explain the anemia upon the basis of blood loss.

The interpretation of this case is difficult. Her response to oral iron and not to oral liver would suggest a hypochromic anemia. The possibility that there is an iron deficiency anemia in combination with pernicious anemia must not be ignored. Without determining the response to parenteral liver to be sure of adequate absorption, this cannot be stated.

There are many instances of idiopathic hypochromic anemia preceding development of pernicious anemia. There is good reason to believe they may coexist.<sup>41</sup> This case is at least significant in demonstrating an antecedent true anacidity four years before the discovery of an apparently idiopathic hypochromic anemia.

*Case 2.* Mrs. B. C., aged 23, whose mother, aunt, and two uncles had proved pernicious anemia (Family J) was seen January, 1938, with her sister. Both had

\* Information obtained through courtesy of Dr. W. A. Richardson, Loma Linda, California.

TABLE IV

Achlorhydria in Near Relatives (Siblings, Children, Parents) and in Distant Relatives (Test Meal)

	No.	No. with Anacidity	Per Cent
<i>Near Relatives</i>			
Conner.....	147	37	25
Kaufmann and Thiessen.....	123	31	17.1
Werner*.....	—	—	19
<i>Distant Relatives</i>			
Kaufmann and Thiessen.....	32	3	9.4
Werner*.....	—	—	9

\* Of 525 tested, 19 per cent of near relatives had anacidity, 9 per cent of distant relatives. The number in each group was not given.

TABLE V

Achlorhydria in Relatives (Test Meals)  
A compilation of all tests not classified as to age groups.

	Number Examined	No. with Anacidity	Percentage
Conner.....	154	40	25.9
Neuburger.....	29	1	3.4
Weinberg.....	24	10	41.7
Zadek.....	46	10	21.7
Wilkinson and Brockbank.....	38	9	23.7
Dorst.....	6	2	33.3
Queckenstedt.....	4	1	25
Kaufmann and Thiessen.....	167	26	15
Werner.....	525	58	11
Martius.....	4	3	75
Totals.....	997	160	16

TABLE VI

Percentage of Incidence of Anacidity in Various Decades of Life (Test Meal) of Relatives

Age (Years)	Per Cent of Anacidity		
	Normals (5204) (Bloomfield and Polland)	Near Relatives (141) (Kaufmann and Thiessen)	Near Relatives (141) (Conner)
20-29	5.3	17	13.5
30-39	9.5	16	20
40-49	16.7	15	46
50-59	24	31	29
60-plus	35.4	29	50

The most significant finding is the agreement on a definite increased incidence in the 20-40 age period. Conner found an increased incidence in all ages.

histamine gastric analyses. Mrs. B. C. showed true anacidity; her sister had normal free acid. Mrs. B. C. gave a history of having had stomach trouble since the age of 18, characterized by generalized abdominal pain, nausea and vomiting. Attacks would last several hours and came every few nights; they were not apparently attributable to food or nervousness. Her periods had appeared at 14 and had been regular and not painful or profuse. In 1935 she had had a normal delivery. In 1936 her appendix had been removed with no improvement. In 1937 she started eating yeast cakes three times daily and after two months had no further stomach trouble although she had had trouble continuously for a year prior. Her blood count in January, 1938, showed 9.8 gm. hemoglobin, 5.2 million erythrocytes, 8,500 leukocytes.

In March, 1940, she was located in a neighboring city and gave the following history:

In May, 1938, she felt so weak she went to a health clinic. At that time her hemoglobin was 59 per cent (Newcomer), erythrocytes 4.99 million. The blood smear showed "severe anisocytosis and poikilocytosis, an occasional normoblast, many microcytes." She was given reduced iron capsules and liver injections (Lilly) two c.c. twice weekly. Despite the treatment her blood count October 13 was 61 per cent hemoglobin (Newcomer), 4.47 million erythrocytes. She was moving away and was given liver extract powder to take, and although her blood count did not rise abruptly she said the treatment "helped her immensely in every way." Her stomach trouble left, her appetite returned, her strength came back to normal. She moved to San Bernardino, and in January, 1939, began to tire again. She again was given liver injections by her sister, two a week for three months, and again gained normal strength. She took no iron capsules after August, 1938.

In January, 1940, she again had injections twice weekly for six weeks (Lilly's concentrated liver extract, 2 c.c.). These have relieved her nausea.

For the last two years she had complained of a raw, sore tongue which was relieved entirely by liver. She also said that when she was tired out her hands and feet felt as though "they were going to sleep." She had mentioned the tongue to her mother who had remarked that that had been one of her early symptoms.

March 18, 1940, one month after a six weeks' course of liver injections, her blood count showed hemoglobin 15.4 gm., erythrocytes 5.17 million, mean cell volume 85.1 cubic microns, mean cell hemoglobin 29.7 micrograms, color index 1.02, volume index .98.

She looks in good health. She says she always picks up a great deal after having liver. There are no abnormal neurological findings.

This case is unusual in that the blood picture was definitely hypochromic and should have responded to iron, and yet her improvement seemed to follow the use of liver.

#### DISCUSSION

Over a six year period of observation, four of 10 histamine anacid relatives have developed apparent incipient pernicious anemia; two hypochromic anemia; three are in good health with normal blood; one cannot be located.

Early cases necessarily cannot be proved by criteria applicable to advanced cases. The four cases believed to be incipient pernicious anemia were proved to be macrocytic in three. In one the diagnosis was thought justifiable due to the clear-cut history of glossitis and paresthesias relieved by liver.

## POTENTIAL CASES OF PERNICIOUS ANEMIA

Save in negligibly rare cases, true anacidity is always found in pernicious anemia and must necessarily precede its development. Those relatives with a pernicious anemia genotype should show histamine refractory anacidity for a variable period prior to manifestation of the anemia itself. The finding of anacidity justifies at least the suspicion of potential pernicious anemia. The presence of free acid indicates that there is little immediate risk of its development.

## THE HAZARD OF TRUE ACHLORHYDRIA IN RELATIVES

Anacidity in an ordinary individual represents a negligible hazard as regards the risk of later development of pernicious anemia. Bloomfield<sup>39</sup> says the risk is one in three or four hundred. No statistical data are available to measure the hazard of achlorhydria in relatives of pernicious anemia patients. What percentage are prepernicious anacidities cannot be stated.

Until a practical test is devised to interpret the anacidity in terms of deficiency of Castle's intrinsic factor, we will have to base our prognosis upon studies which indicate the number of anacid relatives who later develop the disease. Only observations of large numbers over a long period of time can furnish dependable data of this nature.

It will probably be found that in such a study of the relatives of a case of pernicious anemia, those found to have anacidity will prove eventually to comprise most if not all of those who develop pernicious anemia. This should be especially true when the group studied falls in the age group of the fifth and sixth decades.

Close observation of such a large group would not only establish the comparative hazard of true anacidity in the relative but would lead to an early presumptive diagnosis before development of marked blood and nerve changes. This would constitute a definite step toward the prevention of pernicious anemia.

## STUDY OF PERNICIOUS ANEMIA FAMILIES

In the last six years we have adopted a tentative scheme for the study of families in which pernicious anemia was present.

We arbitrarily have accepted heredity as the most important etiological factor, and thus justified our consideration of the family as the unit of greatest potential concentration.

We have attempted to locate manifest pernicious anemia in other family members by detailed histories, personal investigations and correspondence with the attending physicians.

Ten families were discovered with two or more having the disease, and 10 were collected from fellow internists in Los Angeles. In 18 of these 20 families the familial occurrence was proved, in two it was based on hearsay.

5. Four of the 10 have developed incipient pernicious anemia. Two have developed idiopathic hypochromic anemia.

6. Two relatives who refused gastric analyses developed pernicious anemia with severe spinal cord damage.

7. The development of severe pernicious anemia and of its neurological sequelae can be prevented in many instances if all anacid relatives are considered as being potential cases of the disease.

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*Family 2.* Mr. D. S., aged 65 years, has been under treatment for pernicious anemia since 1926, when his life was saved by the discovery of liver therapy. His sister came to ask about him in 1934. At that time she was in good health but was asked to have a gastric analysis done, which she refused. In February, 1939, Mr. D. S. mentioned that his sister, now aged 70, living in a neighboring city, was unable to walk because of "arthritis," and that she had a "peculiar anemia, but not pernicious anemia." She was seen and found to have diminished reflexes, diminished senses of vibration and position. She was unable to walk without holding on to a chair. She had been on oral liver and iron capsules and her count was 3.9 million erythrocytes, 80 per cent hemoglobin (Sahli), 6,200 leukocytes with slight macrocytosis in the blood smear. She was given liver parenterally; 20 c.c. reticulogen (Lilly) over a period of three weeks. In six weeks she had improved so that she could walk without a cane. At the present time her blood count is normal, but she is handicapped by ataxia.

11. Two anacid relatives, one and two years after histamine study, developed early symptoms of pernicious anemia and were relieved by liver treatment.

#### CASE REPORTS

*Patient 1.* Mrs. L. C., aged 42 years, was first seen in 1933 with laryngitis. She said her uncle had died of pernicious anemia. This was proved by a letter from the attending physician. Two aunts were also said to have died of pernicious anemia, but this was not verified. She was in general good health. In 1936 a blood count showed 4.9 million erythrocytes, 9,000 leukocytes; 81 per cent hemoglobin (Sahli), with a normal differential count and blood smear. The gastric analysis after histamine showed true anacidity. Two years later, in July, 1938, she complained of malaise and "beginning arthritis" saying that her hands tingled and her feet felt numb. She had had a sore tongue for several months, which had puzzled her husband, a dentist, since gingival sepsis was absent. The tongue was clean and smooth at the edges. There was no disturbance of sense of vibration or of muscle position. The reflexes were normal. A blood count showed 3.62 million erythrocytes; 10.6 hemoglobin (Sahli). She was leaving for a motor trip to Seattle the next day. An intramuscular injection of 4 c.c. reticulogen (Lilly) was given as a therapeutic test. She returned on September 12, 1938. Her sore tongue and paresthesia had gone. Her blood count showed 4.03 million erythrocytes; 70 per cent hemoglobin (Sahli). Liver injections at intervals have been given and she has had no return of symptoms. In 1940, although having no glossitis or paresthesia a blood study showed definite macrocytosis.

*Patient 2.* Mrs. W. E., aged 50 years, was first seen in September 1937, with Dr. C. G. Toland. She had a moderately toxic diffuse goiter. Her mother had died of pernicious anemia. In 1935 she had been found to have no acid by test meal. We repeated the gastric analysis with histamine and found true anacidity. Her blood count was 4.39 million erythrocytes; 74 per cent hemoglobin (Sahli); 7,400 leukocytes, with a normal blood smear. A subtotal thyroidectomy was done on January 10, 1938, from which she recovered satisfactorily. In July, 1938, she developed numbness in both feet and a sore, burning tongue, for the latter of which she consulted her dentist. He said she was a little pale, and as a coincidence, because his mother had pernicious anemia and took liver, and her mother had had pernicious anemia, advised her to take some liver capsules. She took them regularly and in February, 1939, when next seen, her paresthesia and glossitis had gone. Her blood count showed 4.78 million erythrocytes; 78 per cent hemoglobin (Sahli); 7,200 leukocytes and a normal blood smear. She has refused to stop liver because of the marked improvement.

# THE FUNCTION OF *LISTERELLA* IN INFECTION\*

By L. A. JULIANELLE, *St. Louis, Missouri*

WHEN Sir David Bruce discovered "*Micrococcus*" *melitensis* as the causative organism of Malta fever, there was little evidence to indicate that the future was to unfold a new group of human diseases tracing their origin to animal sources. Yet, as is also true of other bacterial and viral diseases, brucellosis has since become a well-recognized series of manifestations which aptly illustrate the precept that the animal may serve as a reservoir for the dissemination of disease to man. While it may be an imprudent, if not precarious, gesture to attempt prognostication, the contingency nevertheless seems not too remote that medicine may witness another example of a group of infections implanting themselves from animals into man. Thus, there is reason for contemplating that the bacterial genus *Listerella*, now occurring fairly ubiquitously among animals and fowls, is gradually adapting itself to man, with listerellosis becoming in time as common perhaps as brucellosis.

It is primarily with the intention of preparedness, when and if the time actually arrives, that the present communication is being made. Because of studies recently undertaken in this laboratory in this connection, it appears to be an opportune moment to introduce the subject for general discussion and thought. Reviewing, first, the bacteriological properties of the genus *Listerella*, as determined in this laboratory, it is then proposed to discuss briefly the chief characters of animal infection; to present a résumé of verified listerellosis in man; and, finally, to offer for consideration personally acquired evidence both sustaining and opposing the concept that infectious mononucleosis may be an expression of the same organism.

## BACTERIOLOGY OF *LISTERELLA*

*Listerella* (*Bacterium monocytogenes*) was first discovered by Murray, Webb, and Swann<sup>1</sup> in 1926 as the incitant of a spontaneous infection in stock rabbits and guinea pigs. The infection was characterized by mononucleosis, occasional involvement of the mesenteric glands, with focal necrosis of the liver, and fatal termination. Since then, bacteriological studies have been made by other workers.<sup>2</sup> The organisms of this group may grow poorly, so that blood should be added routinely to media for enrichment. In the presence of blood, colonies are small and grayish and are surrounded by a zone of hemolysis. While the organism is a small gram-positive, motile rod, its arrangement together with its colonial appearance causes its confusion with hemolytic streptococcus or diphtheroids.

\* Read at the Cleveland Meeting of the American College of Physicians, April 3, 1940.

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TABLE X

## Analysis of Ten Anacid Relatives with Subsequent Blood Findings

Case	Age	Sex	Date of Gas- tric Anal- ysis	Blood Count	General Health	1938	1939	1940						Blood Sugar	Remarks
								Hemo- globin per Cubic mm.	Hemato- crit per 100 c.c. Blood	Mean Cell Vol- ume	Mean Cell Hemo- glo- bin	Color Index	Vol- ume Index		
1	19	F.	1935	Normal.*	Good.			4.1	12†	30‡	87	29.5	.87	.95	Excellent health.
2	38	F.	1935	Slight anemia. C.I.—1.17.	Good.		Hypochromic anemia. R.B.C. 3.8 mil. Hemoglobin 8.5 gm.	3.97	1.25	Not done.	—	31.4	1.08	—	Fair health. Improvement on iron, not to oral liver. Parenteral liver not given.
3	38	F.	1936	Normal.	Good.	Macrocytic anemia. Sore tongue, parasthesia. Re- lieved by liver.		4.16	13.5	40	96	32.4	1.13	1.06	Fair health. No return of glossitis or parasthesia. Inadequate liver indi- cated by macrocytosis.
4	04	F.	1936	Normal.	Fair. Easy fatigue.			3.69	12.2	36	97.5	33	1.13	1.08	Poor health. Easy fa- tigue. Tongue smooth. Impaired vibratory sense in left leg. No sore tongue or parasthesia.
5	48	F.	1937	Normal.	Toxic goiter.	Sore tongue, parasthesia. Relieved by liver.			Could not be obtained.						Cannot be located. One year ago feeling well on oral liver.
6	33	F.	1937	Normal.	Good.			4.49	13.3	38	80	20.6	.88	.92	Fair health; fatigues easily. "Nervous indigestion."
7	23	F.	1938	Normal.	Fair, easy fa- tigue. Helped by yeast.	Hypochromic anemia. Hemoglobin 8.2 gm. R.B.C. 4.99 million.		5.17	15.4	44	85.1	29.7	1.02	.98	Has taken no iron since 1938. Fatigue and sore tongue; relieved by liver injections last two years.
8	38	M.	1938	Normal.	Good.			5.5	16.4	40	83	20.8	1.03	.93	Excellent health.
9	37	M.	1938	Normal.	Good.				Not located.						Moved to North Carolina. Cannot be located.
10	62	M.	1939	Normal.	Good.			4.24	13.5	42	98.6	31.8	1.08	1.1	Fair health. Is losing weight. Tires easily. No sore tongue or pares- thesia.

\* Normal means red cell count and hemoglobin normal. Packed red cells not determined.

† Hemoglobin determinations by Sahli-Hellige Hemoglobinometer save for (2) in which Newcomer Hemoglobinometer was used.

‡ Packed red cell volume determined by Sanford-Magath tubes. Centrifuge—3000 R.P.M. to constant volume.



gested in a preliminary note on the results with eight strains,<sup>3</sup> the different cultures separated themselves into two distinct immunological types. The pertinent data are summarized in table 1. It will be seen that of 15 strains derived from animals, 4 fell into one type, and 11 into the other. With two exceptions (a strain from a fox, and one from a calf), the different cultures appear to reflect in their type-specificity their ultimate origin, as rodent on the one hand, and ruminant on the other. It is not intended to imply, however, that the "rodent" type comes only from rodent animals, and the "ruminant" type only from ruminant animals; experimental observations in this labora-

TABLE I  
Distribution of Types of *Listerella monocytogenes*

Source of Strains		Number of Strains		
		Studied	in Type I ("rodent")	in Type II ("ruminant")
Rodent animals	Rabbit Gerbillé	2	2	—
		1	1	—
Ruminant animals	Cow	8	1	7
	Sheep	2	—	2
	Goat	1	—	1
Carnivorous animal	Fox	1	—	1
Man	Meningitis	6	3	3
	Mononucleosis	1	1	—
Totals		22	8	14

tory indicate too clearly that rodent animals (rabbits, mice, and guinea pigs) may be fatally infected with strains from ruminant animals. It may be possible, nevertheless, that the original source of a given strain may be determined by the agglutination reaction. However, until further study is made, it cannot be stated whether the suggested relationship of type and animal source is only apparent or actually genuine. It is interesting in this connection that Paterson<sup>2</sup> suggests the possibility of three serological groupings on the basis of flagellar antigens.

The seven strains isolated from man were divided; four into the "rodent" type and three into the "ruminant" type. If the hypothesis formulated above for the serological types be confirmed by future work, it would then serve to indicate the animal derivation of strains found in human infection.

There remains to add that the two types were verified by agglutinin adsorption and specific precipitation of polysaccharides prepared from the corresponding organisms.

Since identification of *Listerella* may be confusing, a test suggested earlier is recommended for purposes of diagnosis. This consists of in-

The development of hypochromic anemia in two cases stresses the tendency of the apparently idiopathic form to appear in pernicious anemia families. Whether there is latent or coexistent pernicious anemia can only be conjectured at present.

The significant feature is that 10 relatives were considered as having potential pernicious anemia while in good health. The appearance of early signs and symptoms in four out of 10 with the possibility of later development in others indicates that the hazard of achlorhydria in a relative is very high.

It suggests the importance of knowing whether a patient with achlorhydria has or has had pernicious anemia in the family.

Since pernicious anemia may occur only in a single generation, the patient may have no knowledge of a family occurrence. It would seem important, for the future, that patients be advised of this hereditary tendency, so that their grandchildren may be able to state positively of this occurrence, thereby placing achlorhydria in that family in the category where pernicious anemia may be suspected as a possible rather than an improbable development. Secondly, the physician should study the family rather than the patient alone. If the disease is familial, or hereditary, the families will contain latent cases.

Those relatives with free acid present could practically be eliminated, and the anacid relatives be watched for early signs and symptoms. It would appear unwise to acquaint them with the early symptoms as it would lead to the promiscuous use of liver and prevent the recognition of the early development.

It is certain that the insidious development of severe spinal cord damage may be prevented in many cases if the relatives of pernicious anemia patients are sought out and grouped by means of the histamine gastric analysis.

The physician's duty is to the family, not to the patient alone.

Macklin<sup>25</sup> has said "the ancestor, immediate or remote, constitutes the forgotten man in medicine." We should go by the rule that the blood relatives of patients with pernicious anemia are potential cases until proved differently.

#### SUMMARY AND CONCLUSIONS

1. Twenty families with two or more members having pernicious anemia have been added to the literature, making a total of 235 families.
2. The increased familial incidence and the available data regarding the disease in monozygotic twins suggest that pernicious anemia is frequently, if not invariably, transmitted by heredity.
3. The incidence of anacidity in relatives of pernicious anemia patients is increased over that in normal groups of the same age and sex. Anacidity is twice as high in near relatives as in distant relatives.
4. Sixty-one relatives were examined by histamine gastric analyses and 10 (16 per cent) found anacid. These were considered as potential cases.

is indistinguishable from *Bacterium monocytogenes* of Murray, Webb, and Swann.<sup>1</sup>

(b) *Ruminant Animals*. Listerellosis in ruminant animals was first reported upon by Gill<sup>7</sup> when he observed the infection in sheep. Clinically, the manifestation suggests a meningo-encephalitis: first, incoördination, and then a tendency to move in large circles, thus contributing to the infection the more common name of circling disease, until the animal drops from sheer fatigue. The spinal fluid is cloudy with an increased cell count, and at post mortem there is seen congestion and meningitis, sections later revealing perivascular cuffing, and less commonly, foci of neutrophiles. The disease has since been studied by other workers,<sup>8</sup> and recently a detailed report has been made by Graham, Hester, and Levine<sup>9</sup> of outbreaks in Illinois. An interesting deviation of the infection in sheep was reported by Paterson when he observed the occurrence of 16 abortions in a group of ewes, apparently caused by *Listerella*.<sup>10</sup>

Jones and Little<sup>11</sup> published the first communication on *Listerella* infection in the bovine species. Since confirmed by Graham and his co-workers,<sup>8</sup> a recent report<sup>9</sup> gives more detailed information concerning several outbreaks of the bovine disease in Illinois. In this species, the infection manifests itself by a staggering gait, paralysis of the mandible, elevation of the head, and finally coma leading to death. The lesion is essentially meningo-encephalitic and cultures of the organism are recoverable from the medulla. The same authors described abortion as another expression of the bovine disease.<sup>9</sup>

While no report has been made of *Listerella* infection in the goat, Seastone<sup>2</sup> has supplied this laboratory with a strain derived from this animal. Paterson,<sup>10</sup> however, quotes Seastone by personal communication that the goat reacts to the disease as does the sheep.

(c) *Carnivorous Animals*. Recently, *Listerella* organisms have been isolated from an outbreak among silver foxes.<sup>6</sup> Apparently the disease must have resembled very much distemper of dogs, since that was the diagnosis made by the veterinarian in charge. The mortality was high, but unfortunately no histological reports are given.

(d) *Fowls*. Listerellosis of fowls was first observed by TenBroeck, the authority for this statement being Seastone,<sup>2</sup> who employed for study some of the former's strains. Since then Seastone,<sup>2</sup> Paterson,<sup>10</sup> and Watkins<sup>10</sup> have published accounts of the infection. In poultry, the chief sign of the disease consists of a massive myocarditis with necrosis, occasionally including the liver. It is the opinion of certain observers<sup>10</sup> that in the fowl, *Listerella* infection is secondary to a primary condition, such as paralysis, leukemia, internal parasitism or concurrent infection.

Thus it is seen that *Listerella* is capable of infecting various species, manifesting in the different animals an almost characteristic selectivity for the different tissues. The mode of transmission from animals of the same or different species still remains to be determined.

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TABLE III  
Fatality of *Listerella* Meningitis in Man

Observer	Date	Location	Number of Patients	
			Reported	Died
Atkinson	1917	Australia	5	4
Tesdal	1934	Sweden	1	1
Schultz et al.	1934	California	1	0
Burn	1934	Connecticut	4	4
Allen *	1936	Connecticut	1	1
Gibson	1936	Scotland	1	0
Carey	1936	Massachusetts	1	0
Poston et al.	1937	No. Carolina	1	1
Wright and MacGregor	1938	Scotland	1	1
Cislaghi †	1938	Italy	1	0
Porter and Hale ‡	1939	Iowa	1	0
Porzecanski and de Baygorria	1939	Uruguay	1	0
Totals			19	12

\* This case cited by Burn.<sup>2</sup>

† Not verified by bacteriological study.

‡ Treated with sulfanilamide, possibly responsible for recovery.

communication,<sup>21</sup> he reported three more successful isolations of the organism. With Schmidt,<sup>22</sup> he restudied the disease by cultures of the spinal fluid, again recovering the bacterium in question.

As reported elsewhere,<sup>23</sup> *Listerella monocytogenes* was identified in this laboratory after recovery by Dr. C. A. Pons from the blood of a patient with apparently typical infectious mononucleosis. This observation stimulated the study to be reported at this point on the possible significance of *Listerella* in this disease. The study was pursued by (a) blood cultures from patients; (b) agglutination tests with the patients' sera, using the two types of *Listerella monocytogenes* as antigens; (c) experimental infection in different animals; and (d) stimulation of "heterophile" antibody by *Listerella* under varied conditions. The diagnosis of infectious mononucleosis in the patients utilized in this study was verified by the clinical signs and symptoms, changes in blood constituents, and "heterophile" antibody—characteristic in each case.

(a) *Blood Cultures.* The blood from 12 patients with infectious mononucleosis was cultured, in some instances three and four times during the course of illness. The blood was seeded in quantities of 2 to 4 c.c. in veal infusion broth alone and with 1 per cent dextrose; also, pour plates were made with 1 c.c. and 2 c.c. of blood in veal infusion agar. The media were incubated at 37° C. for 10 days, when they were studied by staining and plating on blood agar before they were discarded as sterile. Except for the first culture,<sup>23</sup> all the others failed to give any growth.

(b) *Agglutination Tests.* All tests were performed with 18- to 24-hour broth cultures of both types of *Listerella monocytogenes*. In some instances,

In an effort to obtain more fundamental information on this group, 22 strains\* have been collected from various sources, and a comparative study has been made in this laboratory. Cultures have been carried on blood infusion agar or in infusion broth to which was added 5 per cent ascitic fluid and 0.03 per cent dextrose. Almost as good growth, however, may be obtained in tryptose broth (2 per cent tryptose, 0.5 per cent sodium chloride, 0.03 per cent dextrose, and 1000 c.c. water, pH 7.4-7.6). It is interesting in this connection that the strains from ruminant animals appear to grow most heavily, in some cases even profusely.

A study of the reactions in different media revealed no test of diagnostic possibilities. Thus, in sugar media, all strains caused fermentation without gas of dextrose, maltose, salicin, levulose, mannose, rhamnose, and sucrose, while in lactose there was only a trace of acid. No effect was exerted on mannite, sorbite, inosite, arabinose, xylose, adonite, raffinose, inulin, dulcitol, and galactose. Other differential tests, as production of hydrogen sulphide, ammonia, creatinine, indol, nitrates, nitrites, and Voges-Proskauer reaction were all negative. In litmus milk there was slight acid formation with decolorization of litmus, and in gelatin no liquefaction was observed.

As for pathogenicity, all the strains caused death of mice, rabbits, and guinea pigs, following intravenous or intraperitoneal injection. The minimal lethal dose varied from  $10^{-3}$  c.c. to  $10^{-6}$  c.c. of culture for the different strains. Four of the strains were inoculated intravenously in monkeys (*M. rhesus*) in quantities up to 0.5 c.c. of young broth cultures with no visible effect. Further attempts were made to infect rabbits and monkeys by daily spraying directly into the throat, or by nasal, drop by drop, instillation of broth cultures. The inoculations were continued for a week without inducing infection. While it is impossible to calculate the quantity of culture sprayed into the throats of the animals, it is interesting that 0.5 c.c. was instilled each day intranasally in rabbits and 1.0 c.c. in monkeys. The latter dosages were undoubtedly excessive as compared with the quantities injected intravenously or intraperitoneally, so that the conclusion is reasonable that the respiratory route probably plays little part in the natural evolution of the disease. On the other hand, when the cultures were given to white mice by drinking, the animals died of generalized infection, with the organism recoverable from the heart's blood at post-mortem. It would seem, therefore, that infection by the gastrointestinal tract is a possible means of dissemination, as suggested by Murray, Webb, and Swann,<sup>1</sup> and later, Burn.<sup>12</sup>

A serological study, also, has been made of the 22 strains. Antisera were prepared by the immunization of rabbits with both heat-killed and formalized bacteria, the respective antisera showing no essential differences. Tests for agglutination were subsequently conducted and, as already sug-

\* The strains utilized in this study were obtained from Drs. C. G. Burn, H. W. Cromwell, Philip Edwards, Robert Graham, W. M. Hale, N. P. Hudson, F. S. Markham, C. V. Seastone, E. W. Schultz, and H. W. Wadsworth.

human disease, has not been encountered in the experimental infection. Whether this difference is to be considered as an actual deviation from the characteristic change in infectious mononucleosis or a gradation dependent upon differences in the animal species is not clear from the data at hand.

The glandular involvement seen in man is reproduced to a measure.

TABLE IV  
Blood Changes in Non-Fatal Experimental *Listerella* Infection  
Rabbit No. 352

Day of Infection	1	2	3	4	5	6	7	8	9
Total W. B. C.	7,450	12,650	7,550	11,600	15,000	12,000	7,800	12,200	9,650
Neutrophile	41	66	42	40	50	62	40	55	67
Basophile	4	1	3	—	—	8	7	13	3
Eosinophile	—	1	—	—	6	—	—	1	—
Myelocyte	—	—	—	1	—	—	—	—	—
Lymphocyte, mature	47	22	24	21	24	16	31	17	21
"    young	—	2	1	3	2	1	—	3	2
Monocyte, mature	8	8	25	22	17	11	23	11	7
"    stimulated	—	—	4	4	1	2	—	—	—
Clasmatocyte	—	—	1	2	—	—	—	—	—
Total R. B. C. (millions)	4.680	4,250	3.880	—	—	3.620	3.120	3.410	3.950
Hemoglobin (%)	70	57	48	—	—	46	34	31	42

TABLE V  
Blood Changes in Fatal Experimental *Listerella* Infection  
Rabbit No. 354

Day of Infection	1	2	3	4	5	6
Total W. B. C.	12,050	8,400	5,800	19,950	9,800	10,000
Neutrophile	49	70	46	35	40	45
Basophile	3	4	3	7	4	1
Eosinophile	4	—	1	1	2	—
Lymphocyte, mature	35	20	23	15	16	8
"    young	3	1	2	2	6	—
Monocyte, mature	6	5	16	22	27	37
"    stimulated	—	—	8	15	3	14
Clasmatocyte	—	—	1	3	2	—
Total R. B. C. (millions)	5.310	4.600	4.680	—	—	—
Hemoglobin (%)	82	68	64	—	—	—

Participation by the glands in experimental infection is irregular, and the mesenteric rather than the cervical or axillary glands are affected. The splenic enlargement frequently seen in patients was not a characteristic accompaniment of the experimental infection. Histologically it is difficult to compare the tissue changes because of the inadequacy of the reports on the human tissues. Their removal has varied to such an extent as far as the

oculating the eye of certain animals, preferably the rabbit. If the growth is moderately heavy, inoculation may be performed by simple instillation of the conjunctival sac with a drop or two of a broth culture; if, on the other hand, the growth is scanty, inoculation is more successfully accomplished by massaging gently the everted upper conjunctiva with a swab previously immersed in the culture. The inoculation is followed within 24 to 72 hours by an intense conjunctivitis with chemosis, marked exudate, and within a day or two more, invasion of the cornea, represented by infiltration and marked vascularization or pannus. This reaction has been described in detail elsewhere,<sup>4</sup> so that the details need not be repeated at this time. What is important now is that all 22 strains tested induced the reaction, while a large number of other bacteria, including 10 strains of *Erysipelothrix*, a somewhat similar organism, did not. The ocular reaction, therefore, appears to be not only regularly produced by, but apparently specific of the *Listerella* group.

### LISTERELLOSIS IN ANIMALS

While it has been found possible to infect a number of different animals in the laboratory, it seems more logical to confine this brief discussion of listerellosis in animals to the disease as a spontaneous occurrence. For convenience, therefore, the infections will be considered as those occurring in rodent, ruminant and carnivorous animals, and in fowls. The summarized data will be found in table 2.

TABLE II  
Principal Manifestations of *Listerella* Infections

Host		Clinical Condition
Rodent animals	Rabbit	Generalized infection; mononucleosis; glandular and hepatic involvement. " " ; " ; " " " " ;
	Guinea-pig	
Ruminant animals	Sheep	Meningo-encephalitis; occasional abortion. " " ;
	Cow	
	Goat	
Carnivorous animal	Fox	Resembles distemper of dogs.
Fowl		Myocarditis with necrosis.
Man		Meningo-encephalitis; infectious mononucleosis (?).

(a) *Rodent Animals.* As already pointed out,<sup>1</sup> *Listerella* infection was first observed in rabbits and guinea pigs. The disease was characterized by leukocytosis, with a rise in mononuclear elements, and suppression of neutrophils. At death, the predominant changes were focal necrosis of the liver, enlargement of the mesenteric glands, and edema of the subcutaneous tissues.

In 1927, Pirie<sup>5</sup> found a similar infection occurring in South Africa in the gerbille (a small, burrowing animal somewhat similar to the rat). Because the essential lesion was necrosis of the liver, Pirie named the organism isolated *Listerella hepatolytica*, although as later work showed, the organism



In appraising the data acquired in this laboratory on the relation of *Listerella monocytogenes* to infectious mononucleosis, the evidence is not so clear as in meningo-encephalitis. If an analysis be attempted of the individual approaches studied, each appears both to support and to discredit a direct relationship between the two factors. Thus, if the blood cultures be considered, a single recovery of the organism from repeated trials in 12 patients may imply an accidental isolation; yet, on the other hand, it must be obvious that with the disease as mild as it is, invasion of the blood stream by an organism would be an exceptional rather than a uniform occurrence.

In considering the results of the agglutination tests, the supportive evidence is that the sera of roughly half the patients tested caused agglutination of *Listerella monocytogenes*. Since the infection is mild and frequently of short duration, it is possible that insufficient stimulation is supplied by the organism to evoke circulating antibodies. While the low titres may be an expression of the same deficiency, it is also possible that they represent not a specific agglutination, but may be more in the category, for example, of the agglutination of *Brucella* organisms by the sera of patients suffering from tularemia.

As already described, the infection induced experimentally by injection of *Listerella monocytogenes* in rabbits, mice, and guinea pigs does not reproduce exactly the infectious mononucleosis of man. The dissimilarities between the two conditions may imply an actual difference in clinical entity or, instead, a difference in host reactivity to the same agent.

The most serious objection to a genuine relationship between *Listerella monocytogenes* and infectious mononucleosis resides in the inability of the organism to stimulate the formation of "heterophile" antibody, either by prolonged immunization or by active infection in animals responding with high agglutinin titres for the bacterium. Whether the conditions under which the study was undertaken were inadequate, or whether the organism lacks this capacity remains to be determined. Certainly the rabbit, which was particularly studied for this purpose, readily develops anti-sheep cell agglutinin in response to either sheep cells themselves or to heterophile antigen. It may be of further significance that rabbit anti-sheep sera and anti-heterophile sera do not cause agglutination of either type of *Listerella monocytogenes*.

Thus, it seems that the question of *Listerella* in infectious mononucleosis must await future study for a decisive answer. The results thus far acquired warrant further experimentation in order to clarify the problem raised by the isolation of *Listerella* from the blood and the appearance of agglutinins in the sera of certain patients suffering from this disease.

#### SUMMARY AND CONCLUSIONS

1. Bacteriological studies on *Listerella monocytogenes* suggest the ocular reaction of conjunctivitis, corneal infiltration and pannus as a diagnostic test of value.

## LISTERELLOSIS IN MAN

That *Listerella* infection might occur in man was demonstrated unequivocally for the first time by Burn.<sup>12</sup> There is reason to believe, however, that a similar condition and the same organism were actually encountered previously by Atkinson,<sup>13</sup> Tesdal,<sup>14</sup> and almost simultaneously by Schultz, Terry, Brice, and Gebhart.<sup>15</sup> It is interesting that in these three instances, as well as in that reported by Gibson,<sup>16</sup> the organism was classified as a diphtheroid. In Atkinson's and Tesdal's cases, it is assumed that the organism involved was actually *Listerella* from the descriptions submitted, but Schultz and his co-workers subsequently changed their diagnosis to *Listerella*,<sup>2</sup> while Gibson's strain was later reclassified correctly by Webb and Barber.<sup>17</sup> Since the original descriptions by the foregoing authors, other examples of the meningitic syndrome have been given by several workers.<sup>18</sup> It is also possible that the case reported by Cislighi<sup>19</sup> is another illustration, even though no organisms were cultivated from the spinal fluid.

From the literature cited above, it may be said that as a meningo-encephalitic disease in man, *Listerella* infection has been observed in all ages from infancy to maturity, although the majority of cases thus far reported have occurred in young individuals. The principal manifestation consists of a suppurative meningitis, the spinal fluid containing an increased number of cells, particularly of the mononuclear elements. The organisms are seen in smear preparations often ingested by the mononuclear cells. Frequently there is sepsis, which may in turn lead to metastatic pneumonia and focal necrosis of the liver. Unfortunately, blood counts have not been reported in most cases, but where they have been done the indications are that there is leukocytosis with mononucleosis. Histologically, there is inflammation of the meninges, perivascular cuffing, infiltration by polymorphonuclear and mononuclear cells, and hemorrhage; the lungs may show focal pneumonia, bronchiolitis, and atelectasis; the liver discloses areas of focal necrosis, and the spleen undergoes congestion and even hemorrhage.

While a few of the cases reported have recovered in time, the disease has a high fatality. As seen in table 3, 19 cases have thus far been recorded, and of these, 12, or 63 per cent, died. It should be pointed out that the case reported by Cislighi may not have been actually *Listerella* infection, while that of Porter and Hale was treated with sulfanilamide, which may exert a therapeutic effect on *Listerella monocytogenes*, as, in fact, their experimental studies suggest.<sup>19</sup> If, therefore, correction for these two patients is permissible, the fatality is correspondingly increased to 12 deaths in a total of 17 cases, or a mortality of 70 per cent.

RELATION OF *LISTERELLA* TO INFECTIOUS MONONUCLEOSIS

That infectious mononucleosis may be the result of *Listerella* infection was first suggested by Nyfeldt<sup>20</sup> when he isolated *Bacterium monocytogenes hominis* from the blood culture of a patient with the disease. In a later

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several bleedings were made, but when only one test was done the serum used was obtained after the acute phase, usually between the first and second week of the disease. The tests were incubated for 2 hours in a water-bath set at 37° C.; then they were placed in the ice-chest until the following morning when final readings were made. In this way, agglutination tests were conducted with sera from 28 patients. Agglutination was observed in 13 instances, 3 times with the "ruminant" strain and 10 times with the "rodent" strain. The titre was never particularly high, and varied from 1:20 to 1:160. Similar agglutination tests performed with the sera of 50 "normal" individuals or patients with other diseases yielded agglutination on 3 occasions, in titres ranging from 1:5 to 1:20; in each case, only the "rodent" strain was agglutinated.\*

(c) *Experimental Infection.* As stated earlier in this report, *Listerella monocytogenes* is virulent for rabbits, mice, and guinea pigs. Preliminary experiments indicate that monkeys are more or less resistant to the organism, although intracerebral injection may cause rapid death. Murray, Webb, and Swann<sup>1</sup> have already demonstrated that in both spontaneous and experimental infection there is a distinct effect on the blood picture. Thus, without affecting particularly the red blood cells or hemoglobin value, there is a distinct leukocytosis with a rise in the mononuclear elements and marked depression of neutrophilic cells. In addition, there is involvement of the mesenteric lymph glands and focal necrosis of the liver, which may or may not be the counterpart of the jaundice encountered in infectious mononucleosis. In fact, these authors conducted their studies with such thoroughness that it was not anticipated that more could be added to their results and observations. It was more for the personal experience and knowledge that experimental infection was induced in the susceptible animals mentioned above.

The experiments undertaken in this laboratory serve to confirm the studies of Murray, Webb, and Swann. The impression gained here is that while infected animals manifest the blood changes indicated, the picture suggests rather than duplicates that seen in the human. Two typical examples † of the blood changes are given in tables 4 and 5, the former representing a non-fatal and the latter a fatal infection. Both instances serve to illustrate the lymphocytic-monocytic increase induced by *Listerella*. There is, however, a certain quality to the lymphocytes in infectious mononucleosis that has not been reproduced in the animals studied. The so-called Rieder cell—lymphoblastic cell with lobulated, horse-shoe-like nucleus, and pale blue staining cytoplasm containing frequent mitochondria—while common in the

\* Since going to press blood cultures have been studied in five additional patients. These have all failed to yield any growth. Agglutination reactions as described above have been conducted on seven more patients, in each instance the serum causing no agglutination. The statistics at this time reveal, therefore, one positive blood culture in 17 patients studied, and 13 of 35 patients with agglutinins present in low titres. The evidence that *Listerella* may be related etiologically to infectious mononucleosis is, therefore, correspondingly diminished.

† The writer is grateful to Miss Olga Bierbaum of the Department of Medicine of this University for these examinations.

any partial or permanent disability. I quote these figures in an attempt to make clear the great reduction in need for surgical attention. Obviously, although this need is important, it is not nearly as important as many might be inclined to believe.

If surgery, then, is not the major requisite, how important is medical service, defining the term medical service as "medical procedures entirely exclusive of surgical"?

Modern industry is largely chemical and it would indeed be difficult to mention any present-day process of manufacture which is not, in part at least, chemical. The tremendous increase in the use of chemical compounds has brought about greater chances for exposure to not only larger quantities of chemicals but to an almost countless number of new compounds. Taking into consideration the number of compounds in use today, our factual knowledge of their toxicological action covers only a relatively small number. It is only by unfortunate experiences that we have in the past, learned that some of these compounds produce acute and chronic illness or rapid death. Practically all of this knowledge was obtained after all too many individuals had actually become sick or in many instances had died.

Industry's problem is not the *treatment* of occupational diseases, as after all, if one will be truthful about it, most cases of occupational disease get well without any treatment, when removed from exposure. The real problem is the prevention of occupational diseases by recognition of the *very earliest signs and symptoms* which indicate that the employee is getting sufficient exposure to produce physiological changes. When he has passed beyond this stage and pathological changes have occurred, medical protective methods have not been adequate. The actual development of an occupational disease is *an admission of failure* of both medical and engineering protective measures.

The problem, then, *is not how to cure men sick* of an occupational disease, but rather how to protect them against ever becoming ill of the disease; and the administration of any adequate program to accomplish this end must be more than casual—it must be *carefully planned, actively administered* and based upon a foundation of *factual* knowledge.

Obviously, no one can intelligently set up any industrial health protection program that will function adequately, unless he has an exact understanding of the hazards as they exist and a knowledge of the clinical picture which may develop. Industrial methods of production today are often very complex, involving not only the use of numerous chemical compounds but also the handling of these compounds under variable conditions, such as high temperatures and high pressures. The general industrial trend today is to so construct processing equipment as to make the entire operation as nearly closed as possible. With a completely closed process, in which dusts, fumes and personal contacts are reduced to a minimum, there remains always the possibility of leaks and the ever-occurring breakdown which is certain to be followed by exposures which are higher than normal. This is shown by

time element is concerned that the different descriptions show several discrepancies. A conservative estimate would be that although the changes stimulated by *Listerella monocytogenes* in rabbits, mice, and guinea pigs resemble infectious mononucleosis in certain respects, the experimental infection is not a strict duplication of the spontaneous disease.

(d) "*Heterophile*" Antibody. Antisera prepared by the immunization of rabbits with formalinized or heat-killed suspensions of seven different strains (three rodent and four ruminant) were tested by the Paul-Bunnell method<sup>24</sup> for agglutinins active on sheep red cells. In no instance were the sera found to contain "heterophile" antibody, despite their high titre for *Listerella monocytogenes*. Since these tests were first done in this laboratory, similar results have been published by Pisu<sup>25</sup> and Kolmer.<sup>26</sup>

Reflection on this observation suggested that possibly inactivation of the bacterial cell may have inhibited the formation of "heterophile" antibody. It may be, for example, that this antibody represents a response to some substance liberated from the tissue cell during active infection, or it may even be the result of some combination of tissue and bacterial cell. In order to acquire information on this possibility, eight rabbits were infected successfully, four with the "rodent" type and four with the "ruminant" type. Similarly, four monkeys (*M. rhesus*) were also inoculated. Trial bleedings were made up to 10 days, unless the animal died before that time, as happened in three instances. The inactivated sera were later tested for "heterophile" antibody, but agglutination of sheep red cells did not occur. It seems, therefore, that under the conditions stated, *Listerella monocytogenes* of either type is unable to stimulate the formation of "heterophile" antibody.

In attempting to derive an answer conversely, agglutination tests were undertaken with both types of *Listerella monocytogenes*. The sera used for the tests were rabbit antisera prepared by immunization with sheep red blood cells, and with genuine heterophile antigen. While both antisera contained high titres for the blood cells, they were unable to agglutinate either strain of *Listerella*.

#### DISCUSSION

That *Listerella* is the cause of specific infections in various animals and fowls is obviously well-established by studies of the spontaneous disease and its experimental reproduction by several workers. The fact that such infections are widely and frequently distributed in animals suggests that listerellosis is essentially an animal affliction. What concerns the physician directly, however, is the possible spread of the condition to man. There can no longer be any doubt that while the pathways are still obscure, a purulent meningitis caused by *Listerella monocytogenes* is becoming increasingly recognized in man, and that the manifestation, while not so fatal as pneumococcal or staphylococcal meningitis for example, causes a high rate of mortality. There is a possibility, moreover, that the disease may become more commonly recognized than it is at present.

made simply for the purpose of excluding individuals who showed even the most minor physical defects. *Such a program is unfair and if continued will create an insurmountable problem of unemployment.* Anyone who has had experience in doing this work knows that it is impossible to find enough physically perfect men to fill any plant of appreciable size, and physical defects are not often a bar to selected employment.

The employment examination must, if it is to be sufficiently accurate to enable one to properly place applicants, include a chest roentgen-ray, complete urinalysis, a serological test for syphilis, a blood count, and a reasonably accurate estimation of visual acuity for both near and far vision. The Snellen test is by no means satisfactory. Our experience with the telebinocular has been most helpful and from the industrial standpoint it offers the best method available at the present time.

It is not my purpose to go into the details of how to make a physical examination but rather to point out that one is of necessity almost forced to use most of the available clinical methods because of the difference between examining a sick patient and an applicant for employment. Applicants for employment are in general not inclined to give a truthful medical history concerning either their present or past complaints. Their purpose is to convince the examiner that they are physically fit for the job, rather than come to him for treatment of their ills. So they will deny many pertinent facts. This unfortunate condition was largely brought about by the early physical examinations and the indiscriminate rejections. One of our problems now, is to educate the applicant to the realization, that for his own protection and future health there are certain types of work to which he is not suited. For example, applicants with arrested pulmonary tuberculosis should never be employed in positions where they will be exposed to gases and dusts which are known to be pulmonary irritants. Individuals with any circulatory disturbance must be excluded from exposure to certain chemical compounds which we know act directly upon the circulation, and so on, taking into consideration every organ of the body and the possible chances of aggravating any existing disease.

We sometimes find it necessary to reject an applicant for the position for which he has been selected. He then will consult with his family physician who tells him that there is no reason why he should not have been accepted. Undoubtedly his family physician is sincere in making this statement, but unfortunately he has not the proper conception of the risk involved and fails to realize that what was done, was so done for the protection of the future health of his patient. The physician outside of industry finds it hard to understand why we cannot accept cases, which we know are risks, for a trial period in order to observe what happens. Here it must be pointed out that any unfavorable developments in any case of chronic or arrested disease are compensable, as the aggravation of an existing condition. Therefore it becomes readily understandable that in addition to the risk to the employee, there is the added risk of compensation expenses to the employer.

2. The 22 strains studied divide themselves into two distinct immunological types.

3. The infections caused by *Listerella* in rodent animals are for the most part generalized, with mononucleosis and glandular and hepatic involvement.

4. In ruminant animals, the infection is primarily a meningo-encephalitis, occasionally inducing abortion.

5. In the fox, representative of carnivorous animals, the infection appears to be respiratory, resembling distemper of dogs.

6. In the fowl, myocarditis with necrosis is the important manifestation of infection.

7. In man, listerellosis expresses itself with meningo-encephalitis, with a fatality of about 70 per cent.

8. Whether infectious mononucleosis of man is also an example of *Listerella* infection cannot be answered conclusively until further study be made.

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We have another group consisting of 1250 syphilitics, all of whom are gainfully employed; every one is under the care of his or her family physician for adequate treatment. Each one must frequently present satisfactory evidence to show that he or she is getting adequate treatment regularly.

Knowledge of the action of the compounds handled, the symptoms to be expected and the careful selection of applicants who can work under these known conditions safely must always be followed up by periodic physical examination. In this examination lies the most important part of the work, as almost the entire program of prevention is dependent upon these repeated examinations provided they are done with the proper frequency and are of such a nature as to reveal early signs of absorption.

The frequency of the periodic examinations depends upon the rapidity with which the compounds in question may be absorbed and produce symptoms. The type of examination must be such as to reveal the earliest symptoms of absorption, not the symptoms of acute illness. This phase of industrial medicine may truthfully be said to require one with special knowledge and training to organize and execute the program.

In addition to understanding the mode of action and the clinical picture that indicates early absorption, it is important to realize that any examination program must be as practical and as simple as possible. When dealing with a sick patient in the hospital the physician orders blood counts, blood chemistries, roentgen-rays and many other procedures as often as necessary, and the patient submits with more or less complacency. If, however, one attempts to handle a group of workers and asks them to submit to more or less painful procedures too frequently, they will sooner or later rebel. Furthermore, in industry one must always remember that any medical examination must be made on company time and time away from work means loss of money to the employer and increased costs of production. Medical costs are eventually charged against production and an increased cost of even so small an amount as one-tenth of a cent a unit may mean added costs of thousands of dollars over a period of one year. I mention costs because it is quite obvious that medical men, in general, fail to realize the importance of the economic problem. There is in general the feeling that industry should pay regardless of the costs because they need the service. Industry does need the service and will pay willingly if and when it can be convinced of the need for the service, that the service will be the answer to the problem at hand, and will lead to savings in compensation costs and potential medico-legal suits.

The results of the periodic examination determine whether the employee shall continue with his work or whether he should be removed from exposure and placed, temporarily at least, in other work. If he shows signs of early absorption, then the industrial physician must determine whether the faulty exposure is due to general working conditions or careless methods on the part of the worker himself. The latter is often the cause and obviously it is of no avail to recommend an entire change of working condi-

# INDUSTRIAL MEDICINE AS A SPECIALTY AND ITS RELATION TO GENERAL PRACTICE\*

By G. H. GEHRMANN, M.D., F.A.C.P., *Wilmington, Delaware*

DURING the past 25 years the introduction of medical control methods into industry has experienced a more or less stormy course of events. Industry on one side has been rather reluctant to assume its responsibilities for the protection of its employees' health, and the medical profession in general has underestimated the potential possibilities for the development of a new field in preventive medicine, and has been more or less critical of those working with industry to promote the cause. Probably there has been a lack of understanding on the part of all concerned, which, if clarified, may lead to a more coöperative working basis between industry, the medical profession and the industrial medical group.

Any attempt to clarify a situation should be preceded with at least a brief statement of the problem at hand, and in this instance it seems that the starting point might well be a statement of the actual needs of industry. Which is the more important requisite? Is it primarily surgical, or medical? If medical, is it curative or preventive?

In viewing the problem from a surgical standpoint, one must first sketch a rather brief review of the events as they have occurred from the period when industry first began its medical protective program. This time coincides with the introduction of the compensation laws in 1911. These laws made the employer financially responsible for injuries occurring while at work, established fees for the payment of hospital and surgical care, and provided pay for the injured employee. In addition they fixed payments for disabilities and death. This stimulated industry to establish two new services—first aid and safety.

In the early days the demand for surgical treatment was indeed urgent, both for first aid to the more severe injuries and for adequate treatment for minor injuries, such as abrasions, lacerations, contusions and burns. In the treatment of these minor injuries, industry recognized a means of preventing the more serious sequelae which so often follow.

The more severe injuries, requiring extensive home or hospital treatment, were then occurring with great frequency. However, with the development and application of safety measures, there came about a gradual decline in the frequency and severity of accidents. In our own Company, for example, 30 years ago it was not unusual to have 3,000 major injuries over a one year period. During the year 1939 there occurred a total of 112 major injuries among an average of 45,000 employees, spread out among units over the entire country. In many of these units there was not a single accident which was severe enough for a man to lose any time or to result in

\* Read at the Cleveland meeting of the American College of Physicians, April 4, 1940.

# PANCREATITIS: AN ANALYSIS OF TYPES AND CAUSES\*

By KENNETH M. LYNCH, F.A.C.P., *Charleston, S. C.*

THE picture brought to mind by the term acute pancreatitis is that of a necrotic, hemorrhagic gland, in the extreme state gangrenous, which has produced an upper abdominal catastrophe with severe pain and tenderness, collapse and death.

In fact the very names used to designate acute disease of the pancreas carry the significance of extreme disease, thus *acute hemorrhagic pancreatitis* or, more recently in usage, *acute hemorrhagic necrosis*, whereas in actual anatomical study neither hemorrhage nor necrosis of conspicuous degree need be found. Consequently, the older name, *acute pancreatitis* may still be considered a better one to designate the class, reserving qualifying terms for use when they are appropriate.

Since Opie<sup>1</sup> reported the production of acute hemorrhagic pancreatitis by a gall stone lodged at the ampulla of Vater in such a way as to convert the biliary and pancreatic ducts into a common channel for the flow of bile into the pancreas, the usual conception has been that the mechanics of the disease must be of such a nature and that bile is the offending or exciting factor.

It seems timely that attention be drawn to the frequent occurrence of grades of the disease not constituting a major clinical or anatomical catastrophe and, further, to the fact that other causes of pancreatitis than entry of bile or even duct obstruction may be of importance.

Rich and Duff<sup>2</sup> in a comprehensive study of pancreatitis not only drew attention to epithelial metaplasia in the ducts as a possible cause of obstruction but really gave the clue which has led to our conception of the composite manner in which the severe grades of the disease may be developed from several different beginnings.

Their demonstration that liberated trypsin is sufficiently irritating to cause destruction of tissues and in contact with blood vessel walls leads to necrosis and rupture with consequent hemorrhage lays the ground for a conception that from whatever cause secretion may be liberated the tendency is toward a hemorrhagic type of inflammation, but that unless action of trypsin is sufficient to erode blood vessel walls hemorrhage may not be a considerable feature.

Thus one might expect that from the occurrence of several different orders of conditions, while the primary event is not alike, the ultimate development may well be the same and we might expect to see the extreme case of acute hemorrhagic pancreatitis or even the state of gangrene super-

\* Read before the American College of Physicians, Cleveland, April 2, 1940.

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experience. No matter how safely any manufacturing process may be when installed, the medical supervision must still be carefully maintained.

My allotted time makes it impossible for me to discuss the intricate details of the investigations which are a necessary prerequisite in any industry, to the setting up of a medical protective program. In brief, these should include a careful study of the toxicity of the compounds in use, of the actual and potential exposures, and of the character of the clinical symptoms which will indicate early absorption.

The importance of this first step cannot be overstressed. It is indeed distressing to observe the number of industrial units which are in operation today in which the doctor in charge has very little conception of the working conditions within his plant, no knowledge of the toxicity of the compounds in use, and in too many instances has never been through the factory. This type of so-called industrial medicine is usually conducted by the part-time physician who does not seem to fully appreciate his responsibilities. Such a service is unfortunately stimulating in his factory group a false sense of security. The plant manager knows little of his industrial hazards and feels that once he has taken on a physician to manage the medical program, his hazards are then well under medical control. I recently made an inspection of a plant in which there was a hazard due to exposure to a volatile solvent. The plant physician, a very reputable man in his community, had been doing the medical work for several years. He had never gone through and studied the plant. He examined all employees before entering the plant at the time of employment but never repeated his examination after that. He stated very positively that there had been no cases of occupational poisoning in his plant.

Everyone who has studied the solvent employed in the above instance knows that it is toxic, producing both acute and chronic symptoms with severe mental changes. The exposure in this particular plant is sufficiently high to produce numerous cases of chronic illness which can be easily recognized by simple examination methods.

Medical supervision of this type is to be severely criticized. It all too frequently leads to unfortunate misunderstandings with the employee's family physician. The family physician may not be too familiar with his patient's plant exposure, but does know that there is undoubtedly an association between the man's work and his illness. The plant physician on the other hand claims the illness did not occur at the plant.

With an intelligent understanding of existing hazards plus some knowledge of the physical and mental requirements of all jobs in the plant, applicants can be intelligently selected who will fill these jobs with the least possibility of physical damage to themselves. This selection must be made at the time of the employment examination and in this part of the work lies great opportunity for one to develop his diagnostic ability.

In the past, much just criticism has been directed against physical examination of applicants for employment, because these examinations were

Rich and Duff have called attention to the similarity of the arteriolar necrosis of malignant hypertension to that produced by the action of trypsin; also to the occurrence of thrombosis in acute pancreatitis.

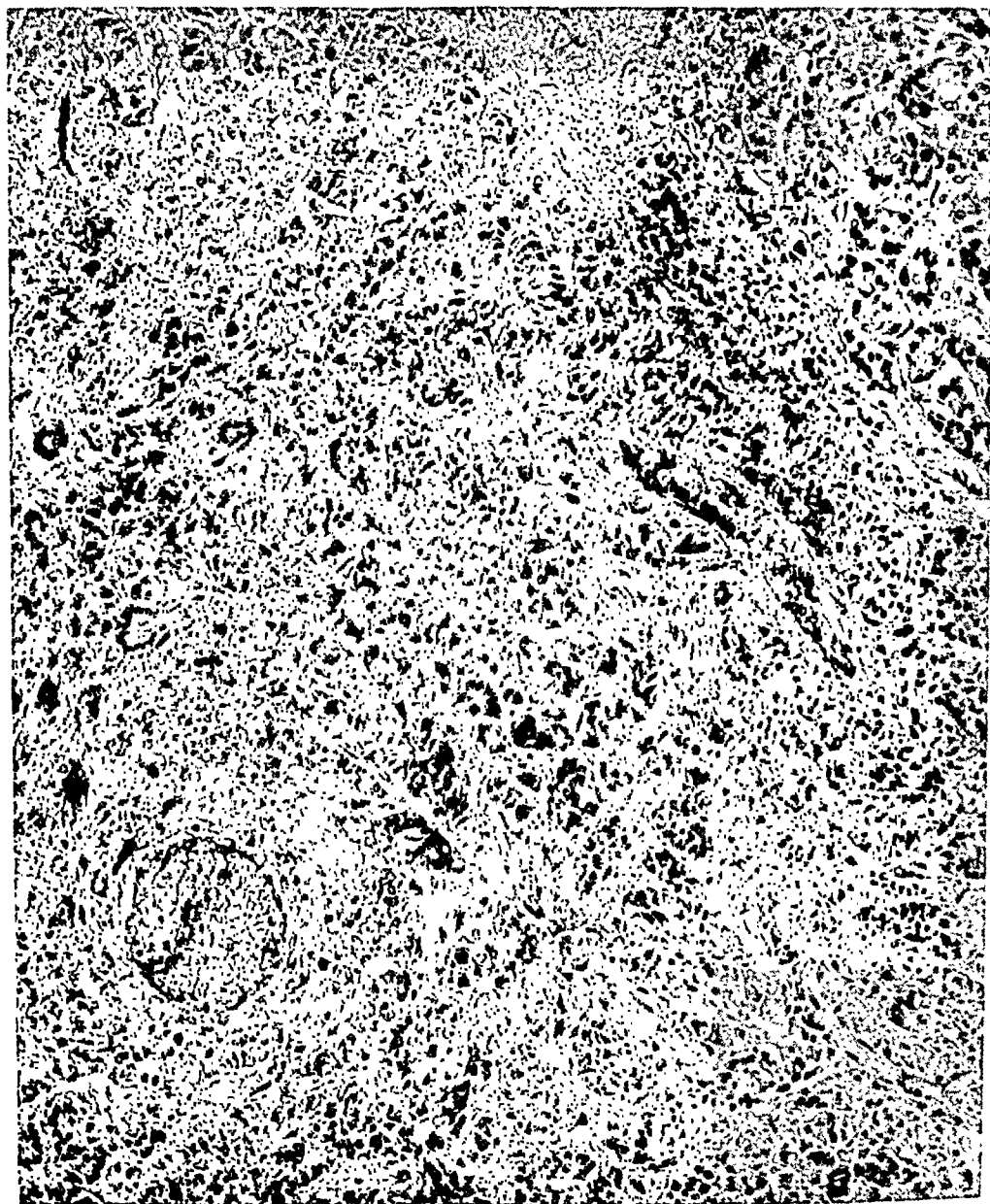


FIG. 1. Acute necrosis of pancreas from vascular occlusion.  $\times 210$ .

In none of these cases was there evidence of duct disease or obstruction, no obstructing condition, no dilatation or accumulation of secretion. Instead there was a massive type of necrosis, with surrounding hemorrhage and active inflammatory infiltration and fat necrosis (figure 1).

These risks are often very high as shown by our experience in aggravated tuberculosis, for example, in which our costs average \$12,000.00 a case.

Under conditions such as have just been mentioned there exists an opportunity for better understanding between the industrial physician and the general practitioner if each will contact the other and discuss the hazards involved in their respective factories and communities. The problems of the chemical industry are too many and too varied for those who are not directly connected with industry to entirely understand. The internist is not expected to render either service or advice, without consultation, to those patients whose ailments fall within the field of the specialist who has studied and been trained in roentgenology, or neurology, or surgery or other specialties.

In any well organized industrial medical service, every employee who is examined, whether it be for employment or periodic checks, is advised to consult with his family physician for the treatment of physical defects or illness found at that time which are not of occupational origin. Industry, in general, is not interested in treating those cases for which they are not responsible and as a matter of fact is only interested in guiding these cases into the proper medical hands in order that they may improve their general health and thereby become more efficient and safer workers. The number of cases referred to the general profession by the industrial physician is truly great. For example, we examined 4200 individuals in our central office during 1939 and over 2000 of these people were advised to consult with their physicians for the correction of existing physical defects or illness. To one who is not experienced in examining a group of so-called well people, these figures might tend to indicate an abnormally high percentage of defects. However, it is indeed amazing when one examines any group of people to find how few, regardless of occupation, do not have some defects that require either surgical, medical or dental attention.

A few figures from the above group will give some ideas as to the incidence of a circulatory disease: 258 had a systolic pressure of 150 or over; 75 had a systolic pressure of 99 or under; and taking 90 as the upper limit of normal diastolic pressure, we found 420 who had 90 or above, some as high as 140; 112 had organic heart disease with audible murmurs. A total, in this group, of 865 showed evidence of circulatory disease.

Thus, in addition to the duties involved in the administration of an adequate medical program for the prevention of occupational diseases, we have the added problem of persuading large numbers of people to improve and protect themselves, insofar as medical aid will accomplish this objective, against acute and chronic diseases while in the early stages before they have become disabled. My purpose in mentioning these cases is to point out to those of the medical profession who persist in maintaining that the industrial physician is robbing them of work which rightfully belongs to them, that they are really having referred to them many cases which would otherwise not be seen until much farther advanced.

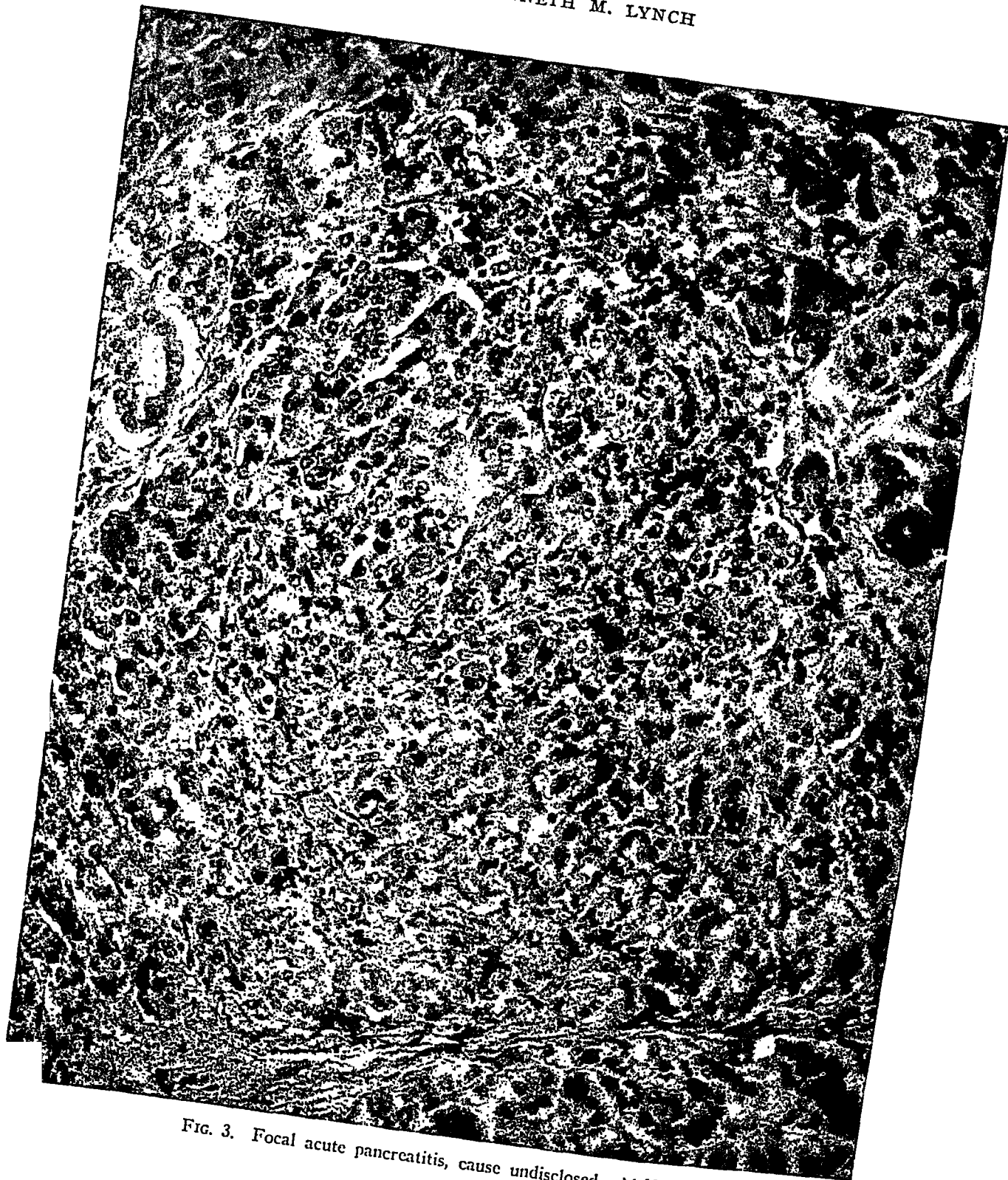


FIG. 3. Focal acute pancreatitis, cause undisclosed.  $\times 300$ .

tions, which will never suffice under such circumstances. It is sometimes necessary to dismiss workers who are consistently careless and thereby constantly subjecting themselves to unsafe exposures.

The follow-up of medical conditions in the plant requires frequent and often prolonged visits to the actual operations where conditions may be studied firsthand. Air analyses are sometimes valuable but should never be used as a criterion of safety. From the medical standpoint, we are interested in knowing whether the men are being affected rather than what the concentrations in the air might be. Air analyses are of value to the engineering department who use them as a guide to determine whether their ventilating devices are functioning according to expectations. It is unsafe to set any concentration of a compound in the air as a safe one unless medical examinations are to be used as an index of health among the men.

In the time allotted to me I have tried to outline briefly some of the major principles of industrial medicine and at least indicate the importance of inaugurating a program based upon an intelligent understanding of the conditions that should be met. Any such program, if it is to be adequately followed, must necessarily require sufficient time on the part of the physician who undertakes it, if he is going to give his best efforts toward the prevention of occupational diseases and the promotion of better health.

If the work is done properly, the examinations made accurately, and the follow-up conscientiously pursued, the opportunity for real, worthwhile, scientific medicine is available. On the other hand, the work can be non-productive of preventive results and scientific interest, and a sheer waste of time, if performed as too much of it is being performed at the present time.

In conclusion the following recommendations are made:

1. Know the toxicity of the compounds and their mode of action.
2. Understand the potential hazards and job requirements on the plant.
3. Select employees who can safely fill the jobs.
4. Watch every one of them by proper periodic examinations.
5. Refer all illnesses and ailments other than occupational to the family physician.



there is no apparent reason for inspissation to occur otherwise it is probably better looked upon as effect and not as cause.

The walls of ducts may be observed to be necrotic, ruptured and leaking secretion. The spreading of the secretion is attended by necrosis of framework and fat, whether or not extension into the glandular tissue occurs. When this does take place the influence is characteristically from the periphery of the lobule inward, rather than central as in the focal group, or rather than *massive* as in the vascular occlusion group.



FIG. 4. Obstructed pancreatic duct.  $\times 210$ .

Hemorrhage is logically a characteristic feature, thanks to the explanation of Rich and Duff, whether it be extensive enough to give the gross findings or not. Even with minor hemorrhage, the smudgy degeneration of blood vessel wall is apt to be seen.

Leukocytic collections are seen about escaped secretion and necrotic tissue, varying in proportions probably with the duration of the state.

The first patient of this group was a white woman, 71 years of age, with carcinoma of the head of the pancreas, there being no recorded findings to tell of the terminal pancreatic state. The next was a negro woman of 45, with an unruptured abdominal aortic aneurysm. The aneurysm was diagnosed, and pain in the pancreatic region was attributed to it. The third was a negro man of 70, with a pancreatic duct stone. This man was a sufferer from general and renal arteriosclerotic disease, the apparent cause

vene from such different beginnings as from duct obstruction, with or without the entry of bile, from vascular closure, or from infection, either primarily of the ducts or outside them.

#### PANCREATITIS FROM VASCULAR OCCLUSION

Interest in application of this idea arose from a case of typical acute hemorrhagic pancreatitis not based upon duct obstruction but upon embolism of the pancreatic artery.

This occurrence was in the case of a white man of 52 years who, after drinking whiskey, suffered an acute abdominal crisis with severe pain and tenderness and collapse. He gave a history of two similar attacks of pain the last several months previously. At necropsy there was massive hemorrhagic necrosis of the tail of the pancreas, without discoverable evidence of duct disease or obstruction, but with infarction from a thrombus-embolus in the supplying artery. The origin of the embolus was a mural thrombus situated upon atheromatous patches of the aorta above the pancreatic artery.

The occurrence of acute pancreatic disease from vascular closure is usually minimized by students of pancreatitis, but with this case as a base for interest, an investigation of necropsy material in our service for the past ten years disclosed two other cases of this origin among a total of eighteen. The suspicion is aroused that occurrences of this order may be more common than we ordinarily believe and that at least some of the instances of acute disease of the pancreas in which no evidence of duct obstruction are found may be really of vascular origin.

One incident in the story of the first case may merit a further word: the fatal attack occurred after drinking whiskey. This association has been noted not infrequently in previous studies of the disease. Weiner and Tennant<sup>3</sup> give alcohol as a probable factor in 66 per cent of 38 cases of acute pancreatitis. Rich and Duff suspect that alcohol may stimulate trypsin production in pancreatic secretion and thus accentuate its action. The drinking of whiskey in the case cited here could hardly have had a bearing upon the embolism; but it may have accentuated the action of released tryptic secretion.

Both of our other instances of arterial occlusion occurred in patients whose primary disease was malignant hypertensive vascular disease. One was a negro man of 36 who in addition to hypertension had old rheumatic heart disease and was further suffering an attack of lobar pneumonia and an unexplained gaseous edema of the arm which had followed the injection of fluid at this site. The other was a negro man of 30 years whose vascular disease was complicated by bronchopneumonia and acute gastroenteritis. In neither was clinical evidence of pancreatic disease observed in life and what part it played in the fatal issue is problematical. In both there was extensive arteriolar sclerosis and arteriolar necrosis in the pancreas, much like that seen in the kidneys in both cases, and there was extensive organizing thrombosis of arteries and veins.

alinized. Probably at the time when she had diabetes there had been a more or less acute catastrophe to acini and islet tissue, leaving many of the latter permanently disabled, for which compensation had occurred in hypertrophy of undamaged islet tissue and probably regeneration of islets also.



FIG. 5. Old scarring of pancreas with hyalinization of some islets and hypertrophy of others. Case of diabetes nine years ago, now recovered.  $\times 52$ .

Duct epithelial metaplasia was very extensive and exhibited the state in various grades of advancement. In the incipency there occurs between the lining columnar cells and the basement membrane nests of polygonal or rounded cells of uniform size, and with uniform nuclei containing a fine chromatin network and a tiny nucleolus. The outline of these cells is not distinct (figure 6). They accumulate into a nodule pushing the lining

## DIFFUSE AND FOCAL PANCREATITIS

In seven of the other fifteen cases the basis for acute disease seemed unrelated to either duct or blood vessel obstruction. In four of them the inflammatory state was interlobular, consisting of diffuse edema and polymorphonuclear leukocytic infiltration of the interstitial tissues (figure 2).



FIG. 2. Acute diffuse pancreatitis, cause undisclosed.  $\times 210$ .

There was no necrosis and no hemorrhage. It seems that the term acute interstitial pancreatitis would be appropriate in these cases. None of them gave clinical evidence of the pancreatic condition found at necropsy, and its importance is of uncertain status.

One of these was a negro man of 21 who died of acute endocarditis, acute nephritis and cerebral infarction. Another was an aged negro man

epithelium inward and causing it to become flattened and finally quite atrophic, it however remaining distinct from the metaplastic focus. In the advanced stage the whole duct lining may be so displaced, although the

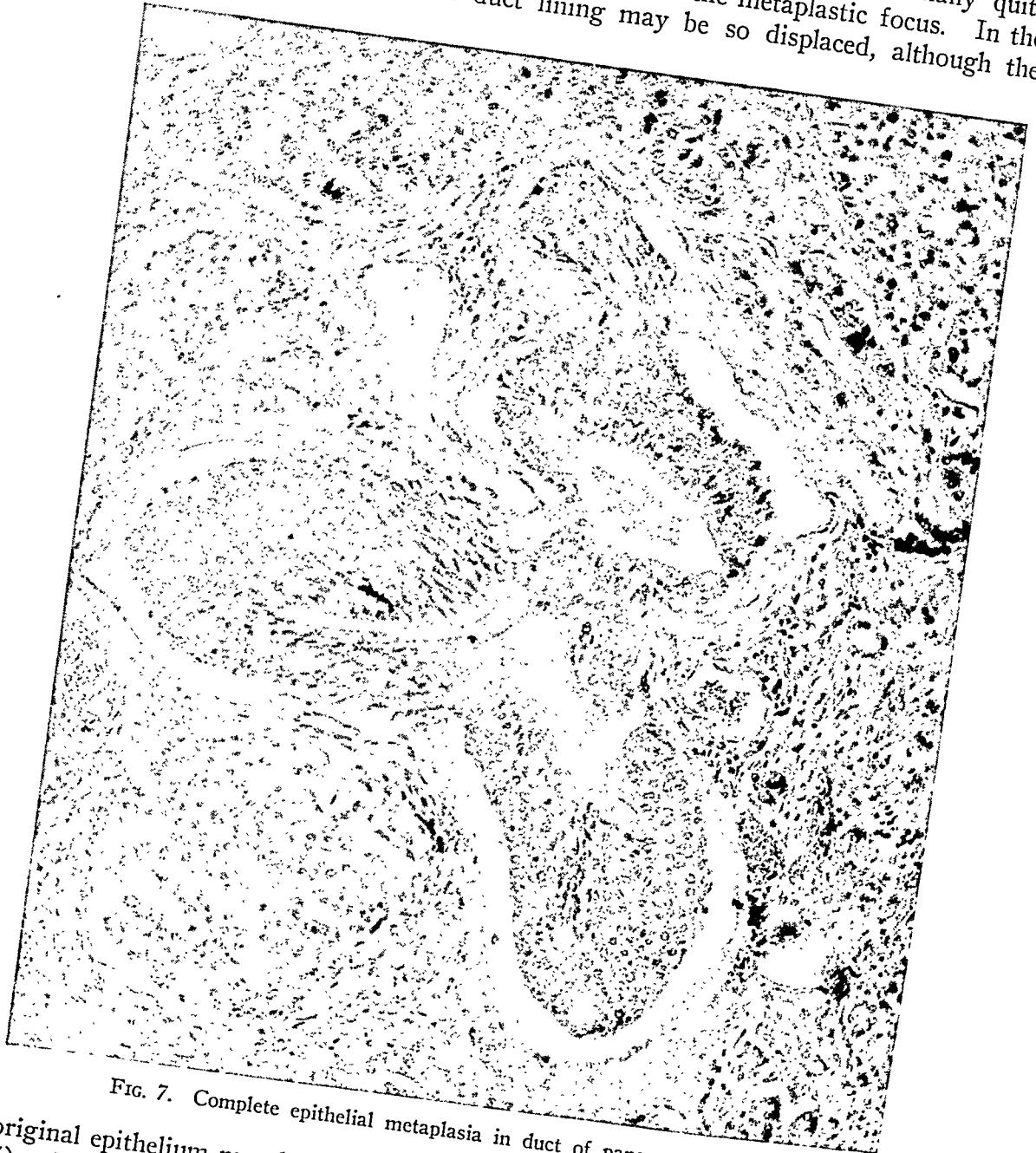


FIG. 7. Complete epithelial metaplasia in duct of pancreas.  $\times 240$ .

original epithelium may be still seen in fragments upon the surface (figure 7). This tends to reduce the calibre of the affected duct. Just how much actual obstruction is thus produced is problematical. In the gland here cited there is little or no evidence of dilatation or of accumulation of secretion, and while it is impossible to say that the scarring

with an infected carcinoma of the pancreas. A third was a negro man with a gunshot wound of the abdomen. The last of the four was a negro woman of 33 with lobar pneumonia, acute pleurisy, acute pericarditis, and tricuspid valvulitis.

The basis for the pancreatitis in two of these four cases seems obviously to have been local infection with extension through the pancreas. The origin of the apparent infection in the other two is not known, but they were both infectious cases. It seems likely that this particular type of pancreatitis is on an infectious basis, and in the extreme grade could well conform to the old class of suppurative pancreatitis. Should ducts become sufficiently involved in such a process there is no reason why the typical picture of acute hemorrhagic pancreatitis should not supervene.

Three of the seven revealed a different picture, that of intralobular rather than interlobular distribution, with small foci of acinar necrosis and leukocytotic infiltration (figure 3). The first was a negro man of 40 with malignant hypertensive vascular disease, atheroma with mural thrombi of the aorta, and abscess of the scrotum. It was a question whether to relate the state of the pancreas to vascular disease, embolism or infection. The second was a negro girl of 12, the only child in the group, and the only case showing duct epithelial metaplasia (not conspicuous). While the pancreatic disease seemed minor in extent and degree there appeared no other explanation for her death. The third was a negro man of 50 with generalized arteriosclerosis, bilateral carcinoma of the kidneys and acute pleurisy.

In none of these three cases were clinical symptoms of pancreatitis observed.

The pathogenesis of this type showing acute focal pancreatitis, is not clear. There was no evidence of duct obstruction in any except possibly the girl. Three modes of development suggest themselves: small vessel occlusion, ductule obstruction, focal infection.

#### OBSTRUCTIVE PANCREATITIS

As would be expected the largest group of the series is undoubtedly based upon duct obstruction. It included eight of the eighteen cases, although in only four was the obstructing condition discovered. In none of the eight was there evidence of such a state as to lead to flow of bile into the pancreas from the bile duct.

The identifying feature of this class of pancreatic disease is obstruction of some part of the duct system evidenced by dilated ducts containing accumulated secretions, whether or not the obstructing object or condition is found. Accumulated secretion may appear in the ducts as smooth hyaline substance or as blobs of coagula mixed with stringy substance (figure 4). Rich and Duff thought that this apparently inspissated secretion might itself be a primary cause of obstruction in some cases, but since it is to be found where some other definite obstructing condition is present and since

of the gland, even of islets was not the product of acute pancreatitis on such an obstructive basis, it does seem that persistence of the metaplasia should have produced persistent effect of the same order, which appears not to be the case.

It is very interesting in this same gland to note the resemblance of the cells in the metaplastic foci to those of the islets. They are very similar, although at times the former are more compact. Of further interest is the occurrence of nodules of unquestionable islet cells in the same basal location as the metaplasia, that is definitely within the duct wall, between the basement membrane and the columnar cell lining and pushing the latter inward and causing its flattening and atrophy (figure 8).

The real nature of this metaplasia is not known. May it be related to an attempt to form islet cells? A further question is, may it not be a part of chronic disease, as other similar epithelial metaplasia may be?

### SUMMARY

Of this series of 18 cases of acute pancreatitis only two apparently gave such clinical evidences of the disease as should have led to a diagnosis of the state. None was actually diagnosed.

In the majority probably recovery would have occurred so far as the pancreatic disease was concerned. This would likely have led to a state of scarring in some degree, a so-called chronic pancreatitis. If this may be true, then is it not likely that similar sub-clinical grades of acute disease of the organ occur as complications of pathological states from which recovery does occur and is this not a logical explanation of the scarring of the pancreas commonly encountered?

While duct obstruction does apparently furnish the main etiological event in pancreatitis it does not appear necessary that it lead to entry of bile nor that bile is at all an essential factor. It appears that vascular occlusion and probably infection cause no inconsiderable proportion of acute disease of the gland. While the lesions produced by these factors are often minor, non-necrotic and non-hemorrhagic, yet these lesions may be sufficient in some instances to cause rupture of ducts and release of secretion into contact with blood vessels. In this event the end result will tend to be identical, irrespective of the pathogenesis. There will be produced that pathological picture which we know as acute hemorrhagic pancreatitis or acute hemorrhagic necrosis of the pancreas.

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of his death, and pain in the right lower chest area was thought to be cardiac. The fourth case was a negro man of 37 who died of chronic nephritis and uremia. The obstructing condition was a papilloma within one of the duct branches. There were no clinical symptoms significant of pancreatic disease. In fact, the lesion was minor in extent, but, curiously, involved hemorrhage into the islets.

Of the four cases showing the features of obstruction, but without discovery of the obstructive condition, the first was a negro girl of 20 with chronic nephritis and abscesses of the liver and spleen. She had suffered severe abdominal pain for two weeks, the abdomen was tender throughout and there was a suggestion of rigidity. She was stuporous and her blood urea was 30 mg. per cent and her creatinine 10 mg. per cent. The next case was a negro man, 57 years of age, with generalized arteriosclerosis and cerebral hemorrhage. There were no symptoms significant of pancreatic disease elicited. The third was a white woman aged 34, a victim of chronic alcoholism. The fatal attack occurred after drinking whiskey. She was irrational and then comatose and exhibited convulsions. There was slight general abdominal rigidity and she would flinch on deep abdominal pressure, but was not aroused. The systolic blood pressure was 170 mm. of mercury and the diastolic 126; there was marked elevation of the levels of blood urea and creatinine. The clinical diagnosis made was uremia. The fourth case was that of a negro man of 60 years with general, renal and coronary arteriosclerosis. Tenderness was elicited over the abdomen and he had pain in the lower right and left sides. He died of progressive heart failure and bronchopneumonia. The pancreas showed typical duct system obstruction but little or no hemorrhage.

#### EPITHELIAL METAPLASIA

The possible importance of duct epithelial metaplasia as an obstructive cause cannot be lightly passed by, even though in a series like this, where particular search was not made throughout the gland, it was seen only once. In those cases where no obstruction is found grossly at necropsy careful section should be made of the gland with this in view.

Weiner and Tennant found metaplasia in three blocks from 63 glands in acute disease, in five blocks from 84 normal glands, and in twenty-four from 114 in fibrous disease, and this apparently from the examination of just one section from each block.

The most conspicuous example I have encountered was in a gland from a woman who died of arteriosclerotic disease with coronary occlusion. She was told that she had diabetes nine years previously, but had apparently recovered. There was no glycosuria or hyperglycemia during her last illness. The pancreas in this case exhibited marked old scarring, with practical obliteration of acini in some lobules, although islets and ducts were present in these same lobules (figure 5). The islets generally were very large, some being apparently normal in cellular structure but many extensively hy-



program consists of adequate exposure to ultraviolet radiation.<sup>6</sup> There is considerable similarity between anemia and rickets (a disease cured and prevented by ultraviolet irradiation when there is an adequate intake of calcium and phosphorus).<sup>7</sup> In both diseases there is lowered gastrointestinal acidity (pH) which interferes with the absorption of calcium and with the absorption of iron, with a resultant decrease in the amount of iron available for blood regeneration.<sup>8</sup> In both diseases changes in the bone marrow and modifications in the types of cells may be seen. Ultraviolet irradiation may be beneficial in the treatment of either disease.

In a study conducted for a period of more than eight years in an artificial light clinic for school children<sup>9</sup> it was found that, in anemic children, after 12 or more exposures to irradiation from a carbon arc lamp the amount of hemoglobin increased by approximately 10 per cent. Another controlled study of the use of ultraviolet irradiation in 54 cases of secondary anemia<sup>10</sup> showed greater increases in hemoglobin and in the number of erythrocytes and leukocytes in the treated than in the control group. It has been suggested<sup>11</sup> that further studies of patients with secondary anemia may indicate a possible influence of ultraviolet irradiation on the chemical constituents of the blood. Although various studies indicate that ultraviolet radiation may be a useful adjunct in the treatment of secondary anemia, there are still insufficient data to indicate the exact value of this therapeutic measure.

In hypertension, various observers<sup>12, 13, 14, 15, 16</sup> have shown that ultraviolet irradiation does produce transient reductions in blood pressure. The work of Laurens and his co-workers in this field has been most convincing. As a therapeutic measure, however, it is doubtful whether ultraviolet irradiation can be considered more than a slight adjunct to the treatment of hypertension.

In carbon monoxide poisoning, ultraviolet irradiation has been employed because of the fact that Haldane and Hartridge showed that the dissociation of carbon monoxide and hemoglobin was markedly increased under the influence of ultraviolet light. Such treatment has been found to be beneficial.<sup>17, 18</sup>

*Diseases of the Respiratory System.* Many articles have been prepared, pro and con, with regard to the use of general ultraviolet irradiation in the prevention and treatment of the common cold. At Cornell University<sup>19</sup> small groups of male students were irradiated with minimal erythema doses of ultraviolet rays once weekly during the winter months. It was reported that there was an apparent reduction of the incidence of colds ranging from 27.9 to 55.5 per cent. At Vanderbilt University<sup>20</sup> an investigation revealed that, in the management of common colds, there was a decided improvement in cases in which ultraviolet irradiation was used.

At the Cook County Hospital<sup>21</sup> ultraviolet irradiation was recommended in the treatment of chronic coughs. It was said to have a stimulating effect on general metabolism and on resistance to infection provided the optimal dose was not exceeded and the patient was free from fever.

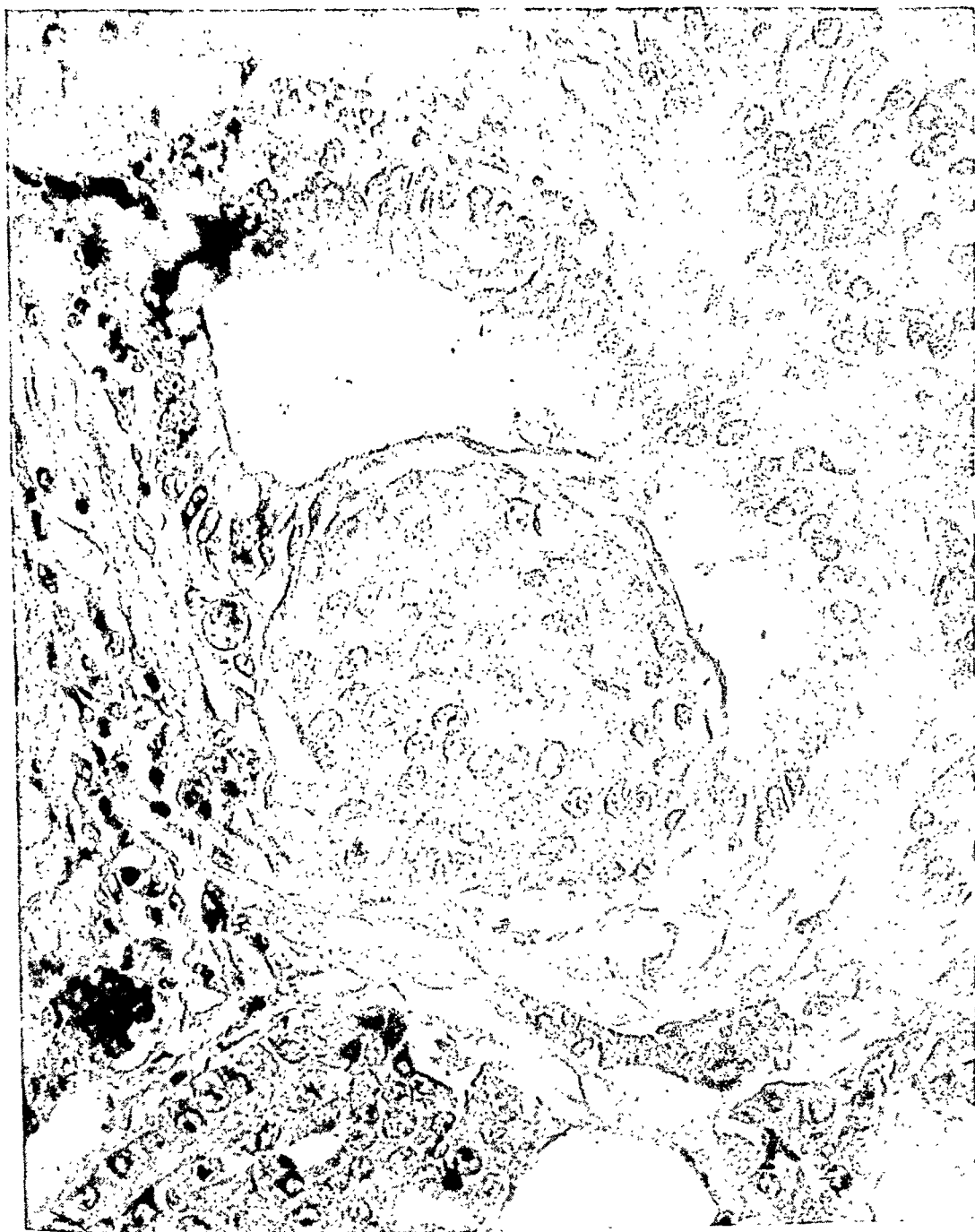


FIG. 6. Nodule of epithelial metaplasia in small duct of pancreas.  $\times 810$ .

Recently a number of writers in the United States<sup>32, 33, 34, 35, 36</sup> have expressed a similar opinion. It has been reported<sup>37</sup> that clinical experience will convince one of the value of the mercury-quartz-vapor lamp in the treatment of pulmonary tuberculosis in children. Tuberculous infants who show excessive pulmonary infiltration even with cavity formation may recover.

Although I believe that, judiciously employed in conjunction with routine institutional care, light therapy may be of value as an adjunct in the treatment of pulmonary tuberculosis, its indiscriminate use is fraught with danger. Of 71 competent observers, 47 obtained favorable and 24 either poor or no results following the use of ultraviolet irradiation in the treatment of pulmonary tuberculosis.<sup>38</sup> This indicates an almost 2 to 1 preponderance in favor of the judicious application of ultraviolet radiation. Far advanced toxic or advancing active, exudative pulmonary tuberculosis should not be treated by light therapy, but incipient pulmonary tuberculosis (especially in children) and nontoxic lesions which have reached the stage of chronicity may be benefited by the careful administration of small doses of general ultraviolet radiation. Abundant rest, an increased intake of food, and proper hygienic measures are more important in the treatment of tuberculosis than is light therapy, which is merely an adjunct to these other measures.

*Diseases of the Bones and Joints.* In a study<sup>39</sup> of 22 children with bone and joint tuberculosis who were treated throughout the winter and spring with radiations from a high-intensity carbon arc light, it was found that the majority showed a rise in the blood count, a tendency to gain weight, and likewise a marked improvement in the local tuberculous lesions.

An extensive study<sup>40</sup> on the nonoperative treatment of tuberculous joints of the lower extremities revealed that, over a period of years, 65 per cent of the adult patients under treatment for all extrapulmonary tuberculous lesions showed a definite, though usually inactive, pulmonary tuberculosis. Conservative treatment by heliotherapy, in conjunction with routine care, was the method used in this large series of cases. Of 437 patients with tuberculosis of the bones and joints and 72 with osteomyelitis (nontuberculous) who remained on an institutional regimen for three months or longer, the following conditions were revealed on dismissal: apparently recovered, 53.8 per cent; arrested, 23.1 per cent; improved, 10.7 per cent; unimproved, 7.8 per cent; died, 4.5 per cent. A follow-up of these patients revealed that between 80 and 87 per cent were working; between 3 and 5 per cent were ambulant but unable to work; and between 3 and 5 per cent were confined to bed. It was concluded that such conservative treatment usually resulted in healing with useful motion. Operative interference should not be attempted until after prolonged heliotherapy has been tried. Bernhard,<sup>41</sup> as a result of 25 years' experience, believed that in the treatment of surgical tuberculosis heliotherapy was the method of choice. In his first 1000 cases of surgical tuberculosis in which patients were treated



FIG. 8. Formation of islet within wall of pancreatic duct. Case of diabetes nine years previously, now recovered.  $\times 515$ .

lesions, and heat, massage and exercise are applied locally to the involved joints.

*Diseases of the Genitourinary System.* It has been reported<sup>57</sup> that in a series of 26 cases following nephrectomy for renal tuberculosis ultraviolet irradiation proved to be a most helpful therapeutic measure for the cure of the tuberculous sinuses and visceral ulceration incident to the disease. It has likewise been said<sup>58</sup> that in tuberculosis of the genitourinary tract surgical treatment frequently offers prompt relief if combined with postoperative heliotherapy.

Direct irradiation of the bladder for the treatment of tuberculous ulceration or cystitis has been recommended by a number of observers.<sup>59, 60, 61</sup>

*Diseases of the Eye.* Following an 18-year study,<sup>62</sup> ultraviolet irradiation was reported to have proved its worth in the treatment of diseases of the eye. Such treatments had, for example, reduced the proportion of losses in *ulcus serpens* from 30 to 6 per cent; ultraviolet irradiations had likewise produced favorable results in other diseases of the cornea, conjunctiva and sclera. Excellent results have been reported in the treatment of corneal ulcers by accurately localized ultraviolet irradiation.<sup>63, 64</sup>

Ultraviolet radiation is likewise often of benefit in the treatment of tuberculous lesions of the eye.<sup>65</sup> A study<sup>66</sup> of the combined use of local and general ultraviolet irradiation for the treatment of tuberculous lesions of the eye in 100 children revealed some improvement in every case.

*Diseases of the Ear.* It has been claimed<sup>67</sup> that irradiation by means of a Kromayer lamp with a small quartz rod will in many instances abort furunculosis of the external auditory canal. Combined local and general ultraviolet irradiations have been reported<sup>68</sup> to be of definite value in the treatment of tuberculosis of the middle ear.

There is little evidence that ultraviolet radiation is of value in the treatment of chronic otorrhea, for which it has occasionally been recommended; it has been pointed out<sup>69</sup> that even a thin layer of mucus or pus will filter out the ultraviolet rays and prevent any favorable action.

*Diseases of the Nose.* Ultraviolet irradiation has been recommended as an adjunct to the surgical removal of tuberculous lesions of the nose.<sup>69</sup> It has likewise been said<sup>70</sup> that ultraviolet irradiation is of value in the treatment of infected wounds and certain nasal dermatoses, and its use has been suggested<sup>64</sup> for ulcerations of the nose, especially septal ulcers. Ultraviolet rays have likewise been said to be of value in the treatment of lupus of the nasal mucosa.<sup>71</sup>

*Diseases of the Throat.* Combined general and local ultraviolet irradiation has been recommended in the treatment of tuberculous laryngitis.<sup>72, 73, 74</sup> Strandberg reported a series of 203 cases of tuberculous laryngitis in which the patients were treated by general ultraviolet irradiation followed by cauterization.<sup>75</sup> One hundred and thirteen patients were reported as cured of the disease of the larynx and the majority of the others were said to have improved. Thomson<sup>76</sup> challenged these results and said that 32 patients

# MEDICAL APPLICATION OF ULTRAVIOLET RADIANT ENERGY \*

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THE use of ultraviolet radiation in the treatment of disease has been most extensive, but much of the literature on the subject has been poorly written and is of an unconvincing nature. It is, therefore, essential that one make a careful analysis of the writings on this subject and accept only that which seems to have proved its claims by properly controlled studies.

## INDICATIONS FOR ULTRAVIOLET IRRADIATION

*Diseases of the Alimentary Tract.* There is now sufficient evidence to indicate that ultraviolet irradiation may be of distinct value in the treatment of tuberculous peritonitis and enteritis. Since this condition is one of the most frequent complications of pulmonary tuberculosis, occurring as it does in from 50 to 80 per cent of all fatal cases, any measure that will be of benefit is of the utmost importance. Ultraviolet irradiation is one of the most important factors in the arrest and treatment of intestinal tuberculosis.<sup>1</sup> In a survey of 8087 routine postmortem examinations, evidence of pulmonary tuberculosis was found in 886 cases and of intestinal tuberculosis in 233 cases. The ratio of pulmonary to intestinal tuberculosis was, therefore, approximately 4 to 1.<sup>2</sup> Of 180 patients with intestinal tuberculosis treated at Saranac Lake, 65 per cent of those treated with ultraviolet light were alive, whereas of those not treated only 17 per cent were alive at the time of the report. At the Trudeau Sanatorium, of a series of 106 patients with intestinal tuberculosis, 88 per cent of those treated by ultraviolet light survived, whereas only 25 per cent of those not so treated survived.

Following the use of the mercury quartz lamp in the treatment of intestinal tuberculosis, tubercle bacilli often disappear from the stools; pain, nausea and vomiting are relieved, but the diarrhea and intestinal disturbances tend to resist the longest.<sup>3</sup>

In the treatment of tuberculous peritonitis the best results are obtained in the ascitic type. In abdominal tuberculous adenitis it may be unwise to temporize with light therapy, since it has been reported<sup>4</sup> that in more than three-fourths of the cases it is possible to excise the affected glands.

Ultraviolet irradiation has been recommended in the treatment of pylorospasm.<sup>5</sup> It is possible that when this condition, as seems often the case, is associated with calcium deficiency, ultraviolet irradiation may be of value.

*Diseases of the Circulatory System.* In the treatment of secondary anemia it has been suggested that one of the important factors in an ideal

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tioned its use for diagnostic purposes,<sup>87, 88, 89, 90, 91, 92</sup> for the identification marking of newborn infants, for the purpose of producing hardening of the nipples prenatally,<sup>93</sup> and for the sterilization of air in operating rooms.<sup>94, 95, 96</sup> It has been pointed out that prenatal irradiation and the irradiation of the nursing mother are efficacious in the prevention of rickets in the child,<sup>97</sup> and that direct irradiation of cows will impart an antirachitic potency to their milk.<sup>98</sup>

### SUMMARY

Ultraviolet irradiation has been used extensively but indiscriminately in the practice of medicine. There is, however, a rather large number of conditions\* in which there is evidence that ultraviolet irradiation is, or gives promise of being, valuable. Among these conditions may be mentioned tuberculous peritonitis and enteritis, calcium deficiency diseases, secondary anemia, carbon monoxide poisoning, pulmonary tuberculosis (as an adjunct), tuberculosis of bones and joints, atrophic and hypertrophic arthritis (as an adjunct), tuberculosis of the genitourinary tract, ulcerus serpens, corneal ulcer, tuberculous lesions of the eye, ear, or nose, nasal ulcerations, tuberculous laryngitis, rickets, and tetany and spasmophilia.

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\* Because elsewhere in this symposium Dr. Anthony C. Cipollaro has discussed the dermatologic aspects of light therapy, the indications for the use of ultraviolet radiation in dermatology have not been discussed in this paper.

On the other hand, some investigators have been of a contrary opinion; thus it has been concluded <sup>22</sup> that although the mercury quartz lamp has been used extensively to enhance individual resistance to colds, well-controlled studies on both infants and adults have nevertheless failed to corroborate claims for its value. Hill and Clark <sup>23</sup> thought that there was little to support the view that ultraviolet irradiation was capable of increasing a person's natural resistance. Still other investigators <sup>24</sup> have performed experiments similar to those conducted at Cornell, with results which were for the most part negative, although they did find that in certain tests the resistance of the irradiated group was greater than that of the control group. Still other investigators <sup>25</sup> observed 363 adults for 35 weeks; during the first 31 weeks approximately half the group were given frequent ultraviolet irradiations, a single minimal erythema dose being applied either to the chest or back at each treatment. The incidence of colds during the period of study was slightly higher in the irradiated group than in the control group; however, it should be pointed out that failure to benefit the treated group may have been due to inadequate dosage. Only a quarter of the body was treated at any session and the dose was not increased at subsequent sessions. It is generally agreed that to produce beneficial systemic effects a series of irradiations of the entire body should be given and that the dose should be gradually increased.

Further investigations will be necessary before final conclusions can be drawn concerning the value of ultraviolet irradiation in treating common colds.

In the treatment of pulmonary tuberculosis there has likewise been much controversy concerning the use of ultraviolet irradiation. Although ultraviolet light is frequently used in Europe for the treatment of pulmonary tuberculosis, in this country it has often been thought to be dangerous. It has been especially stressed that there is danger of producing pulmonary hemorrhage. My own controlled studies <sup>26</sup> on 60 patients who were receiving routine sanatorium care indicated that hemoptysis did not contraindicate the judicious employment of heliotherapy, and a number of other investigators <sup>27, 28, 29</sup> have reached similar conclusions following controlled studies. It has been said that treatment which brings about improvement in the general health of the patient is the best means of combating pulmonary, as well as surgical, tuberculosis.<sup>3</sup>

Observations <sup>30</sup> on 115 patients treated by carbon arc irradiation led to the conclusion that patients with minimal, moderately advanced, and even far advanced pulmonary tuberculosis may be benefited by graduated exposures provided the patient's temperature does not rise above 37.5° C. (99.5° F.) and his general physical condition is satisfactory.

*In Denmark light treatment of pulmonary tuberculosis is now almost universal, and in Britain detailed results in a series of 123 cases led to the conclusion that, provided patients are carefully selected, chronic pulmonary tuberculosis may be treated not only with safety but with good results.*<sup>31</sup>



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by heliotherapy, 858 were "cured," 120 were improved, 14 were unimproved, and eight died, a mortality rate of only 0.8 per cent. Six of the unimproved later died, raising the final mortality to 14, or 1.4 per cent.

In osteomalacia, fragilitas osseum, and delayed union of fractures, all of which may be due to faulty calcium metabolism, ultraviolet irradiation may be of value. In a study<sup>42</sup> of experimental fractures of the fibula in 25 normal dogs and 80 normal rats, measured amounts of carbon arc radiation were administered during the period of healing. During this period 73.9 per cent of the fibulas of animals irradiated with "sunshine carbons," 26.9 per cent of those irradiated with "C carbons," and 41.3 per cent of those of controls, healed. The average healing time for fractures was 3.7 days shorter when the animals were irradiated than when they were not. In fractures of the long bones it has been reported<sup>43</sup> that among patients who were given irradiated ergosterol there was an increase in the density and the amount of callus as compared with a control group of patients. These changes were greatest in children and in the aged, and they began to appear about three weeks following injury. On the other hand, in rabbits and rats given, respectively, 3 and 1.25 gm. of irradiated ergosterol by mouth, there was no increase in the rate of healing or amount of callus in fractures of the tibia and fibula.<sup>44</sup>

In rats on which parathyroidectomy has been performed, with consequent parathyroid deficiency, calcification does not occur regularly in the callus following fracture if calcium is also lacking in the diet; under such conditions irradiated ergosterol promotes calcification of callus.<sup>45</sup>

It seems logical to presume that ultraviolet irradiation has little influence on healthy individuals whose calcium metabolism is normal; but it would seem that it might be of value for patients with faulty calcium metabolism who sustained fractures.

A number of authors<sup>46, 47, 48, 49, 50, 51, 52</sup> have recommended the use of ultraviolet radiation both for atrophic and hypertrophic arthritis. Although there is no specific effect, it is believed by many clinicians that ultraviolet irradiation is of value, particularly when there is an associated secondary anemia or when the patient has been confined to bed for a long period.

It has been claimed that ultraviolet irradiation tends to counteract the decalcifying process in the bones and to have an accessory nutritional influence in managing the anemia, debility and allied conditions so frequently found in chronic infectious arthritis.<sup>48</sup> It has, however, been pointed out that chronic infectious arthritis can continue as a progressive crippling disease even in the Arizona desert unless therapeutic measures other than sunlight and climate are utilized.<sup>53</sup>

It has been recommended that, in cases of chronic infectious arthritis in children, reasonable exposure to sunlight or quartz lights be utilized during the winter months.<sup>54</sup> Ultraviolet irradiation has been especially recommended in the treatment of psoriatic arthritis.<sup>55, 56</sup> A combination of crude, cold tar ointment and ultraviolet irradiations is applied to the psoriatic

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with pulmonary tuberculosis had been treated according to the Finsen plan without any striking evidence of benefit. In only two or three of these cases might some improvement have been claimed.

Nevertheless, Stevenson<sup>75</sup> observed 320 cases of tuberculous laryngitis in which 38 of the patients showed clinical cure, 101 were improved, 81 were unimproved, 59 were worse, and 41 died. All of Stevenson's patients received routine sanatorium care, vocal rest and various local applications to the throat as well as ultraviolet irradiation. It is, therefore, impossible to say which was the most important factor in treatment.

In a study<sup>77</sup> of 452 cases of pulmonary tuberculosis, tuberculous laryngitis was present in 19.2 per cent of the cases. It was felt that reflected sunlight was occasionally of value in supervised cases, particularly during the early stages. It would seem that in tuberculous laryngitis general and local ultraviolet irradiation, in conjunction with routine care, may be of some value in selected cases and is certainly worthy of trial. Several observers<sup>78, 79, 80</sup> have felt that the local applications of ultraviolet light were a valuable adjunct.

*Miscellaneous Diseases.* In rickets it is believed<sup>81, 82, 83</sup> that ultraviolet irradiation furthers the absorption from the intestine of either phosphorus or calcium, or both. It is probable that the hydrogen-ion concentration is the limiting factor in such action. It has been shown by a number of investigators that, to produce beneficial effects in the treatment of rickets, it is necessary to administer only comparatively small doses of effective ultraviolet radiation. For example, a single weekly exposure to one erythema dose of ultraviolet rays was sufficient to produce healing of rachitic lesions in infants.<sup>84</sup> Irradiations with a mercury quartz lamp, front and back, for four to five minutes once weekly until approximately 100 minutes of exposure had been given, was sufficient to effect cure in a series of 43 rachitic nurslings.<sup>85</sup>

Irradiation, even with heavy doses of ultraviolet light, did not prevent rickets in rats which had been placed on a ricket-producing diet provided they were prevented from licking their fur or eating their excretions. If, however, the rats were shaved, the skin sterol was then activated by irradiation, absorbed, and exerted antirachitic effects.

It has been shown<sup>86</sup> that the pro-vitamins D exhibit pronounced ultraviolet absorption. Of the 8 to 10 pro-vitamins D which are said to exist, only two, ergosterol and 7-dehydro-cholesterol, appear to be very common. When irradiated, these pro-vitamins become extremely active, since 5 mg. of either are equivalent in potency to one liter of good cod liver oil. Direct irradiation of the skin by ultraviolet rays may be specific in the treatment of rickets.

Results comparable to those obtained in the treatment of rickets may also be obtained by the use of ultraviolet irradiation in cases of tetany and spasmophilia.

Among the unusual applications of ultraviolet irradiation may be men-

side the left mid-clavicular line in the fifth interspace. The sounds were of extremely poor quality and lacked the characteristic normal snap. The rhythm resembled the so-called tick-tick type previously described by Beck.<sup>15</sup> The first apical sound was equal in intensity to the second and the second aortic equalled the second pulmonic. The rate was 125 per minute. The patient was conscious and to a great extent had recovered from his initial shock. Hourly blood pressure readings were as follows:

On Admission—	112/56	8th hour	— 84/46
1st hour	— 80/20	9th hour	— 98/70
2nd hour	— 64/?	10th hour	— 96/50
3rd hour	— 70/20	11th hour	— 98/56
4th hour	— 76/20	12th hour	— 98/50
5th hour	— 80/30	13th hour	— 96/44
6th hour	— 84/28	14th hour	— 96/45
7th hour	— 85/60	15th hour	— 98/48

Serial electrocardiographic studies showed the following (figure 1):

- June 1: A low  $T_1$ ; inverted  $T_3$ ; high take-off of  $T_4$  (1) and  $T_4$  (2).  
 June 7: Increase in the voltage of  $R_1$ ,  $T_1$ ,  $T_2$  and  $T_3$ ; the latter showing a tendency to be upright;  $T_4$  (1) showed a return to a normal take-off and  $T_4$  (2) showed a low voltage and was notched.  
 June 13:  $T_1$  was diphasic;  $T_3$  was now upright;  $T_4$  (1) showed a low voltage and was inverted;  $T_4$  (2) showed a low voltage and was notched.  
 June 23:  $T_1$  was almost iso-electric;  $T_4$  (1) was upright and notched.  
 June 30:  $T_1$  was beginning to be upright and the  $T_4$  was low and notched.  
 July 19:  $T_1$  and  $T_3$  were flat and of low voltage.  
 August 2:  $T_4$  (2) was inverted.  
 September 7:  $T_4$  (1) was upright and  $T_4$  (2) was still inverted.  
 November 7: Essentially the same as September 7.

The patient remained at the hospital for about five months and was examined repeatedly. The heart sounds except on one occasion were noted as faint, distant, muffled and of poor quality. The blood pressure rose to 110 mm. mercury systolic over 60 mm. diastolic and remained at that level. The final diagnosis was a fractured spine, fractured ribs, a transverse traumatic myelitis and contusion of the heart caused by a direct nonpenetrating trauma.

*Comment:* A contusion of the heart was suspected because of the type of injury, quality of the heart sounds, the tick-tick rhythm, the initial falling arterial blood pressure and the changing electrocardiographic picture. The precordium did not show any signs of injury nor did the patient have any cardiac complaints. It was impossible to determine how much cardiac function had been lost because of the bedridden condition of the patient. The diagnosis rested on demonstrable objective findings.

*Case 2.* H. M., a 17-year-old boy, was admitted to the surgical service of the Flower-Fifth Avenue Hospital on June 3, 1938. While trying to walk on a picket fence he lost his balance and fell a distance of four feet, striking his breast bone sharply against a picket point. He immediately felt nauseated, vomited, and experienced a great deal of difficulty in catching his breath. These symptoms continued and interfered seriously with the patient's ability to carry on his ordinary activities. In the past a heart murmur had been noted, but direct questioning indicated that cardiac compensation had not broken down.

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*Comment:* This boy was in good clinical cardiac health until he sustained a direct nonpenetrating injury of the chest. Immediately afterwards he developed signs and symptoms of mild cardiac insufficiency. This damage was temporary as judged from the examination at the end of four months. This injury evidently was capable of producing the aortic diastolic murmur, the high pulse pressure and the associated changing electrocardiographic picture.

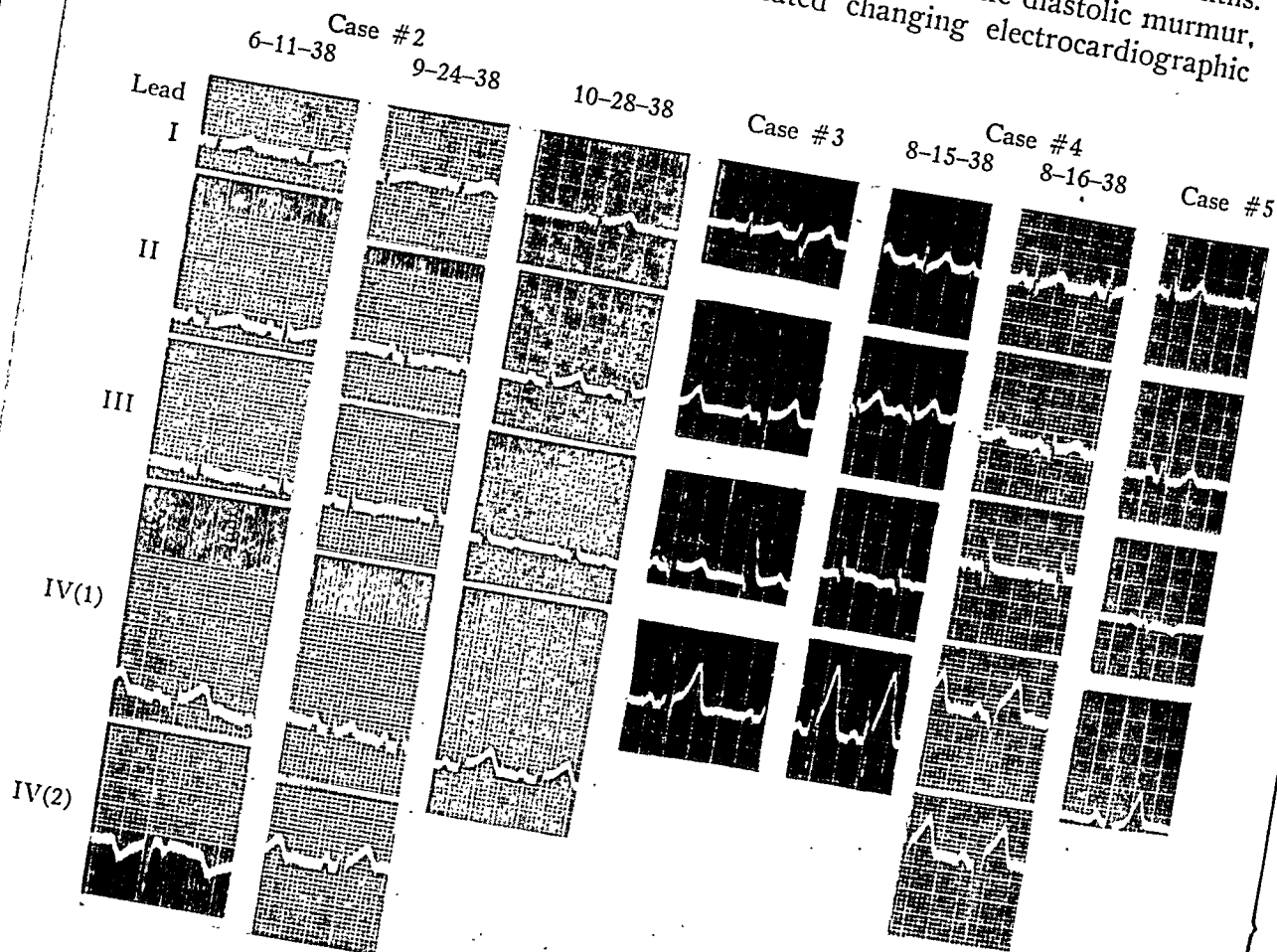


FIG. 2

*Case 3.* J. S., a 21-year-old white male, had always been in good cardiac health until he sustained an accident on June 28, 1938. His chest was caught and crushed between two type cases, each weighing approximately 300 pounds. After the injury he felt very weak and dizzy, and was conscious of substernal and generalized pains in his chest. No fractures were present. He was treated with bed rest and sedatives. On attempting to work, he became markedly dizzy, heart conscious, short of breath, very pale, broke into a profuse sweat and complained of substernal pressure. These symptoms persisted and were aggravated by any exertion. The heart was normal in size, the sounds were of good quality and showed the normal relationship to each

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genographic examination failed to show any fractures. At this institution the examination of the heart and the Wassermann test were negative. He was discharged, but continued to complain of precordial distress, increasing shortness of breath, and an inability to carry on his previous work. These symptoms were progressive and made worse by any kind of exertion. Although the patient has been repeatedly examined, no definite objective findings were present until four months after his injury. He had always been in good physical health, was married, had six children who were living and well, and denied lues by names or symptoms.

The precordium showed a pulsating area about 2 cm. in diameter located in the second interspace about 3 cm. to the right of the sternum. Over this area there was a systolic thrill and a loud harsh systolic murmur which was transmitted to the neck. There was an increase in the area of supracardiac dullness which extended to the above pulsation. The heart was small; the sounds were of good quality; and normal sinus rhythm was present. The blood pressure on the right was 110 mm. mercury systolic over 70 mm. diastolic and on the left 112 mm. mercury systolic over 68 mm. diastolic. The rest of the examination was essentially normal. The roentgenographic studies showed a normal heart shadow with a moderate diffuse enlargement of the aorta and a saccular aneurysmal dilatation of the ascending portion which in the oblique position pointed anteriorly. The electrocardiogram suggested myocardial damage. The Wassermann and Kahn tests, which had been negative, now were strongly positive. The final diagnosis was luetic aortitis with an aneurysm of the ascending portion of the aorta.

*Comment:* This patient was in good clinical health until he sustained a direct nonpenetrating injury of his chest. He then developed cardiac symptoms though repeated examinations did not reveal any obvious pathology until four months later, when the Wassermann test became positive and objective signs of an aneurysm appeared. It is logical to assume that the injury started a chain of events culminating in the above described picture. The exact mechanism of the trauma is a matter of conjecture though it is possible that the aorta may have been injured locally and thus produced a vulnerable spot for the syphilis to localize in.

*Case 6.* S. G., a 49-year-old male, had always been in good cardiac health. On October 9, 1937, he fell from a 12-foot ladder striking his head, shoulders and chest. He was admitted in an unconscious state to the Broad Street Hospital and remained there eight days complaining of dizziness, headaches, nausea, heart palpitation, precordial distress, nocturia and frequency. The above symptoms had not been present before the accident, and continued to persist after his discharge. He was married, had three children who were living and well. His wife had not had any miscarriages, though 25 years previously he had been treated for a chancre.

The eyes reacted to light and accommodation. The heart was enlarged to the left; the sounds were of good quality and normal sinus rhythm was present with a rate of 90. The first apical sound was louder than the second and the second aortic was greater than the second pulmonic. The superficial chest and arm veins were enlarged and pulsated. This phenomenon had always been present. The blood pressure was 100 mm. mercury systolic over 60 mm. diastolic. A definite Romberg's sign was present. The Wassermann test was strongly positive. Radiographic studies showed a dilatation of the first portion of the aorta. The electrocardiograms were essentially normal except for a high take-off of T<sub>1</sub>. The diagnosis was luetic aortitis and possibly myocarditis. Six months later there was a further decrease in cardiac efficiency with the development of an intracranial thrombosis.

# DIRECT NONPENETRATING INJURIES OF THE HEART\*

By HARRY D. LEINOFF, M.D., *New York City*

THE increasing physical hazards and strains of civilization have served to stress the importance of trauma as a cause of disease. The medical evaluation of this factor as it pertains to cardiology is so confused that it is not unusual to find equally competent observers on opposite sides of the same question. This paper is presented as a clinical study of only one aspect of this problem, namely, direct nonpenetrating injuries of the heart.

A survey of standard<sup>1</sup> and specialized texts<sup>2</sup> leaves the impression that this clinical entity is either seldom diagnosed or else is very rare; and in the current literature only is the subject considered to any extent.

Direct nonpenetrating injuries of the heart may result from a blow, a kick or punch over the precordium, the striking of the chest against hard objects, crushing injuries of the thorax with or without fractures, steering-wheel type of accident, sudden compression of the abdomen, the jarring of the chest contents as in falls from a height and perhaps from massive doses of roentgen-rays applied locally.<sup>3</sup> There are usually external signs of injury such as redness, swelling, discoloration, increased local heat and, fractures of the bony parts, but usually no direct open path between the skin and the heart. In the young and occasionally in the older individual the heart may be severely damaged by this type of injury without any local signs.<sup>4, 5, 6, 7, 8, 9, 10</sup> Bright and Beck<sup>7</sup> have demonstrated that fatal cardiac damage may follow the application of a nonpenetrating force to any part of the chest or abdomen<sup>11</sup> and also exploded the popular fallacy that only diseased organs can be damaged by direct trauma. In all types of heart injuries it may be safely stated that the more extensive the trauma, the more extensive the damage. In the laboratory<sup>7, 10, 12, 13, 14</sup> and at the bedside it has been demonstrated that diseased organs tolerate less trauma than healthy structures. This fact aids in understanding why in given instances a minimum of trauma may produce a maximum of change.

## CASE REPORTS

*Case 1.* W. P., a 13-year-old boy, was admitted to the Flower-Fifth Avenue Hospital on May 29, 1938. One hour before he had fallen from the roof of a five story building into the street below. He was in shock, semi-conscious, had multiple fractures of the right ribs, seventh and eighth dorsal vertebrae and an associated complete transverse myelitis. Twenty-four hours later he was examined by the medical service and at this time did not have any cardiac complaints.

The movements of the right chest were decreased and associated with marked tenderness and diminished breath sounds. The left lung showed exaggerated normal vesicular breathing. The heart was enlarged to the left and the apex was just out-

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*Case 9.* H. B., a 46-year-old male, had always been in good physical health until he sustained an accident on January 12, 1937. He slipped and fell striking the left chest and breast against the sharp corner of a machine. He experienced a great deal of pain and was unable to catch his breath for some time. From that time on

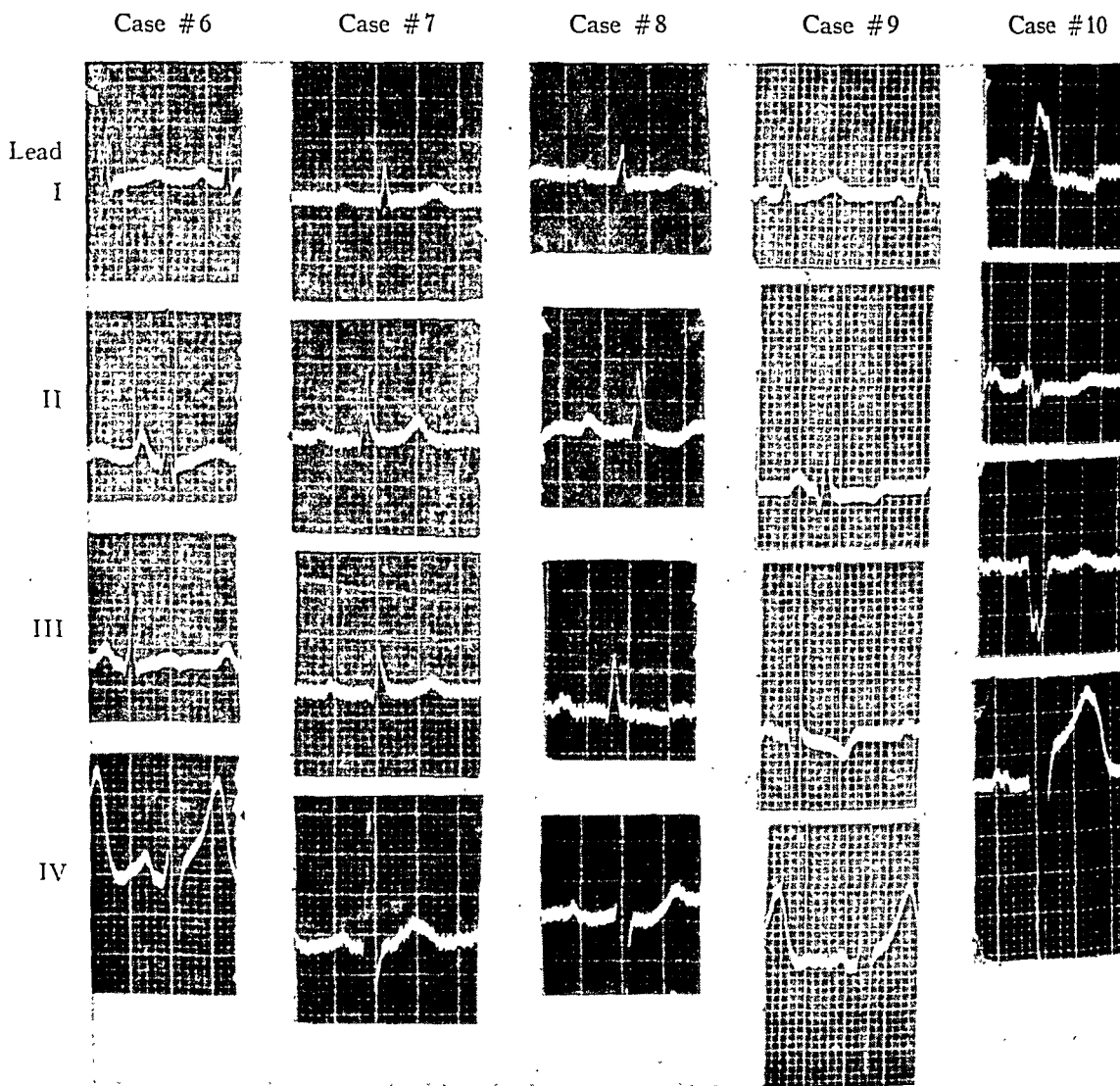


FIG. 3

the patient was heart conscious and complained of precordial pains and some shortness of breath particularly after physical exertion. These symptoms continued intermittently, were progressive in nature and five months later culminated in the complete collapse of the patient caused by an accentuation of the above symptoms. He was institutionalized with a diagnosis of coronary thrombosis. The electrocardiogram showed an inverted and coved  $T_2$  and  $T_3$  associated with a  $Q_2$  and  $Q_3$ .

The heart was normal in size and shape. The sounds were of fair quality but somewhat distant. Normal sinus rhythm was associated with a rate of 86, and a short systolic murmur was heard over the apex. The first apical sound was equal

The examination showed a swelling the size of a small egg over the lower end of the sternum. The roentgenogram revealed a transverse fracture of the lower segment of the gladiolus of the sternum. The heart was enlarged to the left; the sounds were muffled, distant, and lacked the characteristic normal snap. The first apical sound was equal in intensity to the second and the second pulmonic was louder than

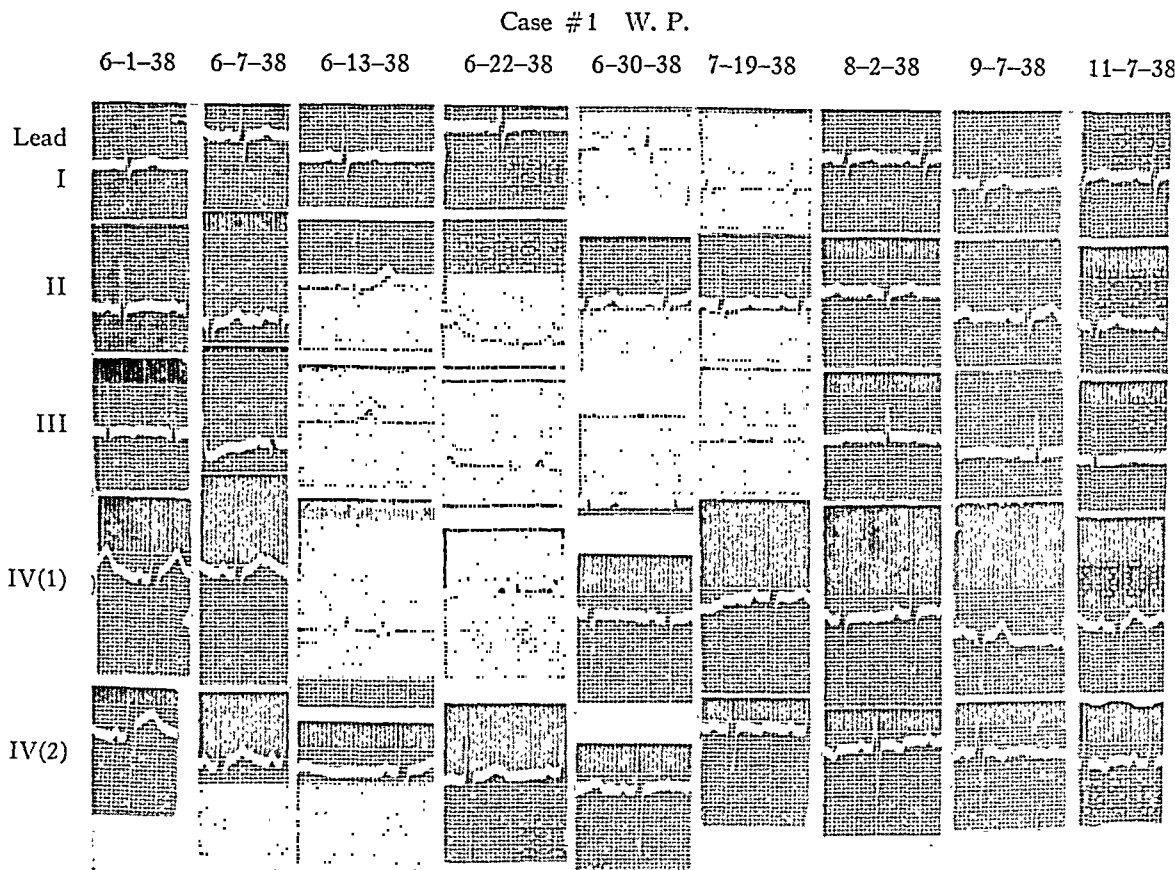


FIG. 1

the second aortic sound. A short diastolic murmur was present over the aortic region. Normal sinus rhythm was associated with a rate of 96. The blood pressure was 110 mm. mercury systolic over 0 mm. diastolic. The rest of the examination was essentially normal.

The electrocardiographic findings (figure 2) were as follows:

June 11: An inverted  $T_2$  and a high take-off of  $T_4$ .

September 24: Inversion of  $T_2$  and  $T_3$ , a more normal take-off of  $T_4$ .

October 28:  $T_2$  and  $T_3$  were upright and a higher take-off of  $T_4$ .

Four months after his injury the patient had fully recovered, with no cardiac complaints. The apex of the heart was located in the mid-clavicular line; normal sinus rhythm was present; the rate was 78; and an occasional extra systole could be heard. The sounds were of fair quality; the first apical sound was louder than the second and the second aortic was greater than the second pulmonic. The diastolic murmur which previously had been heard over the aorta was now heard over the pulmonic region. The blood pressure in both arms was 110 mm. mercury systolic over 60 mm. diastolic. A simple bending exercise was normally performed.

- A. One case—rupture of all the heart chambers.
- B. One case—a tear of the tricuspid valve extending into the auricle and involving the mouth of the superior vena cava.
- C. Five cases—showed subendocardial hemorrhage in the left ventricle and, in some, associated hematomas of the heart muscle and the pericardium.
- D. One case—acute dilatation of the left ventricle.

Though this experience is too limited for any definite conclusions, yet it can be stated that direct nonpenetrating injuries of the chest can and do produce heart damage in a fair number of instances. An awareness of the clinical concept is necessary for the proper diagnosis.

Sex: All the patients in this group were males. In the large series collected by Bright and Beck<sup>7</sup> and in those examined at the Medical Examiner's office a fair number of females were encountered. The predominance of the male is probably due to the greater physical exposure of that sex.

Age: The youngest patient was 13 and the oldest 66. In the older group more serious and lasting damage usually followed.

Predisposing Factors: In the experimental laboratory,<sup>12, 13, 14, 16</sup> it has been demonstrated that artificially diseased hearts tolerate less trauma than healthy organs. This has also been observed at the bedside and in order to evaluate any given case it is necessary to consider the previous health of the organ involved. In this small group an underlying latent condition was demonstrated or suspected in eight out of the 10 patients.

Cases 1 and 3. Normal.

Case 2. Healed rheumatic endocarditis.

Case 4. Questionable polycythemia vera and coronary sclerosis.

Cases 5 and 6. Latent syphilis.

Cases 7, 8 and possibly 9. Coronary arteriosclerosis.

Case 10. Coronary sclerosis and thrombosis.

Pathology: In the nonpenetrating and non-fatal injuries our understanding of the pathological findings which may result rest primarily on the laboratory work of Moritz and Atkins, Bright and Beck, Schlomka, Kulbs and Strauss. The lesions are usually single or multiple hematomas of the heart and its coverings, which are associated with microscopic and macroscopic lacerations and subendocardial hemorrhages. It is interesting to note that this type of injury may damage the superficial coronary arteries and produce signs of infarction or give rise to subsequent cardiac symptoms (case 9). The experimental work stresses the disturbances of function and this to a great extent finds a parallel at the bedside.<sup>18, 19, 20, 21, 22</sup> This latter aspect of functional disturbances can be best demonstrated by an analysis of the 25 animals which were used by Moritz and Atkins.<sup>16</sup>

a. Eight animals—no change.

b. Five animals—extra systoles

other. After a simple bending exercise a faint systolic murmur was heard at the apex and the pulse rose to 180, but did not return to normal within three minutes. The normal sinus rhythm was disturbed by numerous extra systoles which were not abolished by exercise or pressure over the carotid sinuses. The blood pressures were normal. Radiographic studies were normal. The electrocardiogram showed numerous extra systoles of nodal origin.

*Comment:* This patient was in good clinical cardiac health until he sustained a direct nonpenetrating injury of the chest. He immediately developed symptoms associated with extra systoles and a tachycardia. Though the exact pathology in this patient's heart is a matter of speculation, yet it must not be forgotten that a fair percentage of experimental animals showed extra beats after direct injuries.<sup>12, 16, 7, 13, 14</sup> It is possible that an irritable myocardium resulted. Though the consensus of opinion at present indicates that extra beats are usually the result of tobacco, tea, coffee, fatigue and psychogenic influences, yet to this list should be added the possibility of a traumatic origin. These extra systoles did not account for the clinical syndrome, and the final diagnosis was a cardiac neurosis in association with an effort syndrome.

*Case 4.* G. P., a 38-year-old male, was first seen on October 14, 1938. While surfbathing a week previously he was struck in the chest by a large wave and thrown over. On arising he felt sharp pains in the heart region which radiated to both shoulders. In spite of treatment these pains continued intermittently and on October 15 became very sharp and crushing in nature, and were associated with severe sweating and weakness. The past history was essentially normal.

The patient was well developed with a rather ruddy complexion. The heart was normal in size; the sounds were of good quality and had the normal relationship to each other. Normal sinus rhythm was present with a rate of 120. The blood pressures were normal. The fluoroscopic examination suggested a slight enlargement to the right. The electrocardiographic findings were low and slurred QRS complexes in all limb leads and a tachycardia. There was a beginning Q<sub>3</sub>, a definite Q<sub>3</sub>, a high take-off of T<sub>2</sub>, T<sub>3</sub>, T<sub>4</sub> and a low R<sub>4</sub>. Electrocardiographic studies the next day at the Flower-Fifth Avenue Hospital revealed further changes (figure 2) which served to confirm the clinical impression of an acute coronary closure. The blood count was 111 per cent hemoglobin, color index 0.69, red blood cells 8,100,000, white blood cells 21,000, polynuclear leukocytes 84 per cent, lymphocytes 7 per cent, monocytes 9 per cent.

*Comment:* This patient was in good clinical health until he was struck in the chest by a wave. Immediately after his injury he developed signs and symptoms of a coronary thrombosis. Though his injury was not severe, extensive pathology developed. It is possible that he had an underlying blood condition which resembled polycythemia vera, though similar blood pictures may follow a coronary closure. In addition there may have been some coronary sclerosis. The trauma was the exciting factor.

*Case 5.* A. F., a 55-year-old male, fell from the top of a ladder on July 3, 1937 and struck his chest. He was stunned, unable to move, and complained of severe pains throughout his chest. He was removed to a city institution where he remained for 10 days with the above complaints and a laceration of the right shoulder. Roent-

3. In young chests the heart actually may be compressed between the sternum and spine.

4. Immediately preceding an injury the patient automatically fixes the chest in inspiration by closing the glottis and thus produces an excellent medium for the transmission of trauma from the chest wall to the internal viscera.

5. Sudden increases in the intravascular pressures may force the blood back into the heart with sufficient force to damage the endocardium and other layers of the heart. In the postmortem material which was studied sub-endocardial hemorrhages were found only in the left heart suggesting that a sudden back pressure was capable of producing this lesion.

6. The amount and type of heart damage depends upon the quality and quantity of the trauma.

7. Trauma may be the activating factor in initiating potential disease.

8. One or a combination of these factors may act to produce heart damage.

**Clinical Considerations:** Experimental and clinical observers have demonstrated that direct nonpenetrating injuries of the chest can produce fatal and non-fatal damage to the heart. In determining the clinical rôle of trauma it would be ideal if heart studies could be obtained before and after an injury. Unfortunately, this is impossible and it is necessary to draw conclusions after damage has occurred.

The past cardiac status of the patient can be determined by careful direct questioning. In medical-legal cases the history as obtained by the first examiner should be given the greatest weight, inasmuch as the stories of some patients change as time goes on, especially with the aid of unethical legal and medical guidance.

In this group the past histories were essentially normal except in cases 2 and 10. The former had a healed rheumatic lesion with no impairment of function and the latter a previous attack of coronary thrombosis. All the patients except case 10 gave a history of a direct nonpenetrating injury of the chest.

Objective and subjective signs of cardiac damage appeared immediately after the injury, except in case 8 who was bedridden. This point is worth stressing, since the subsequent appearance of heart trouble without bridging signs or symptoms would weaken the possibility of a traumatic origin. The subjective symptoms depend to a great extent on the kind of damage and the associated loss of function. Pain, shortness of breath, exertional heart consciousness were the most common complaints.

The objective findings, particularly in the laboratory, would be encountered more often if the possibility of traumatic heart damage would be kept in mind. In case 1 there was an increase in the size of the heart, distant sounds, the presence of a tick-tick rhythm, a failing pressure and changing electrocardiograms. These findings to a lesser degree were also

*Comment:* This patient was clinically well until he sustained a nonpenetrating injury of the chest. He then developed progressive signs and symptoms of cardiac insufficiency. Syphilis was the underlying cause while trauma was the precipitating or exciting factor.

*Case 7.* L. K., a 55-year-old male, was in good cardiac health and had been employed as a plumber for a great many years. On December 8, 1936, he fell from the top of a six foot ladder and struck his chest sharply against the floor. This injury caused him to vomit, left him weak and produced a sensation of pressure over the breast bone and in his abdomen. These symptoms continued and were aggravated by physical exertion. A progressive shortness of breath began to develop, and approximately six weeks after his injury the patient collapsed completely. At this time, the electrocardiograms showed severe myocardial damage and a first stage heart block. After a prolonged bed rest the above symptoms still persisted.

The left pupil was larger than the right; the eye grounds showed a moderate sclerosis. The heart was normal in size and the sounds were of poor quality. Sinus rhythm was present with a rate of 65. The first apical sound was equal to the second and the second aortic was equal to the second pulmonic. The blood pressure on the right was 130 mm. mercury systolic over 85 mm. diastolic, and on the left 150 mm. mercury systolic over 85 mm. diastolic. Roentgenographic studies showed a mild dilatation of the ascending aorta with a normal heart shadow. The electrocardiographic studies showed an increased P-R interval with some slurring of the QRS.

*Comment:* The patient was in good clinical cardiac health until he sustained an injury. He then developed progressive signs and symptoms of a cardiac nature which finally culminated in an acute episode. There was probably a fair degree of coronary sclerosis which can be considered as the underlying factor, and the trauma precipitated clinical heart disease.

*Case 8.* J. B., a 66-year-old white male, had been in comparatively good cardiac health until he slipped on some icy stairs and fell, striking his upper back rather severely and sustaining a fracture of the transverse process of the fourth lumbar vertebra. In bed his only complaints were pain in the back and nervousness, but exertional shortness of breath appeared when the patient was allowed up.

Moderately advanced generalized arteriosclerosis and a coarse intention tremor were present. The heart was enlarged to the left; the sounds were of fair quality with an occasional reduplication of the first sound at the apex. The first apical sound was equal to the second and the second pulmonic was greater than the second aortic. The liver was palpable at the rib margin. The blood pressure in the right arm was 130 mm. mercury systolic over 50 mm. diastolic and in the left 180 mm. mercury systolic over 86 mm. diastolic. The Wassermann test was negative. Fluoroscopy revealed a moderately enlarged left heart and dilatation of the aorta. The electrocardiogram showed a slurring of the QRS, a low take-off of T<sub>1</sub>, and a P-R interval which measured 0.28 sec. (digitalis).

*Comment:* Though elderly, this patient did not develop clinical heart disease until after his injury. No cardiac complaints were present while in bed, but cardiac symptoms did appear when he was allowed up, at which time the heart enlarged and decompensation developed. The trauma should be considered as a precipitating or aggravating factor and the arteriosclerosis as the predisposing cause of the patient's present condition. Though the actual mechanism is not clear, yet a definite clinical connection between trauma and effect is present.



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in intensity to the second and the second aortic was greater than the second pulmonic. The roentgenogram was essentially normal and the electrocardiogram showed myocardial damage with residual signs of a posterior coronary occlusion.

*Comment:* This patient was well until he sustained a direct trauma to his chest. Cardiac symptoms then began and persisted until he collapsed with a coronary occlusion five months later. In trying to reconstruct the picture only the possibilities can be indicated. The heart may have been traumatized and a small area of hemorrhage resulted. This vulnerable spot may have been the starting point of his acute episode. On the other hand, a coronary vessel may have first been injured and subsequently became thrombotic. This patient was too young to be considered as an arteriosclerotic without any reservations. It was felt that the injury and the linking symptoms indicated that trauma was the exciting etiological factor.

*Case 10.* H. G., was a 50-year-old male, with a history of a coronary thrombosis in 1933. After his recovery he had been able to carry on without any marked impairment of cardiac function. On February 24, 1938, his nose was fractured and a bilateral hematoma resulted. Immediately after this injury pains developed in the chest and the pulse became very rapid. He experienced difficulty in carrying on his routine activities and complained of the precordial distress.

The heart was enlarged to the left; the sounds were of poor quality and lacked the characteristic normal snap. A soft systolic blow was present over the apex. The second apical sound was louder than the first and the second aortic was greater than the second pulmonic. The blood pressure was 120 mm. mercury systolic over 80 mm. diastolic. Roentgenographic studies were essentially normal. The electrocardiogram showed myocardial damage, a typical bundle branch block and residual signs of an anterior coronary closure. These findings were essentially the same as in 1933.

*Comment:* It was necessary to evaluate the results of a single trauma in a known cardiac. The trauma was directed to the nose and face and produced an increase in the subjective symptoms of the patient. It is reasonable to suppose that the injury only produced an aggravation of the subjective symptoms without any objective changes.

## DISCUSSION

*Incidence:* No accurate statistics are available concerning the frequency of cardiac damage which follows direct nonpenetrating injuries of the chest. In a previous investigation of this subject heart damage was demonstrated in two out of a group of six chest injuries.<sup>17</sup> Through the courtesy of Dr. Thomas A. Gonzales, the chief medical examiner of the City of New York, studies were undertaken to determine the frequency of acute cardiac damage following fatal automobile accidents. The protocols of 50 non-selected and consecutive cases were examined, and in eight (16 per cent) definite macroscopic findings of damage were demonstrated as listed below. (These cases are to be reported at a later date.)

rapid diabetic control, even in severe cases, and has in our experience successfully averted the most disagreeable features formerly encountered with the use of protamine zinc insulin. Diurnal glycosuria was apparently more readily controlled; nocturnal reactions were avoided; the need for supplementary regular insulin was obviated; the simplicity of management with protamine zinc insulin alone was gained. Since our original experience with the controlled cases here presented we have used the new regimen in all patients who are taking protamine zinc insulin. We present at this time this preliminary report of our methods and results with representative diabetic patients of various ages and with different degrees of the illness, in the hope that a more intensive trial by other observers will thereby be stimulated.

#### BRIEF REVIEW OF PERTINENT LITERATURE

The early reports on the use of protamine insulin which appeared in 1936 were, on the whole, uniformly favorable.<sup>1, 2, 3</sup> Yet, at that time, Allen<sup>4</sup> alluded to the annoyances he had encountered with the new product. Later, Joslin,<sup>5</sup> Lawrence and Archer,<sup>6</sup> and others<sup>7, 8, 9</sup> pointed out the difficulties that detract from the simplicity of diabetic control with protamine zinc insulin. It is noteworthy that after two years of trial there is a consistent note of discouragement in the reports, notably in the recent papers of Ralli,<sup>10</sup> and of Boyd and their co-workers,<sup>11</sup> which emphasize only the disappointing features of protamine zinc insulin and the difficulties connected with its use. The actual danger connected with the use of protamine insulins, i.e., the danger of fatal reactions, has only recently been stressed in the pointed editorial warning which appeared in the *Journal of the American Medical Association*.<sup>12</sup>

Primarily, protamine insulin was introduced to simplify treatment, i.e., to provide one injection daily instead of the three or four that had been required with the use of regular insulin. Experience has indicated, however, that a single daily dose of the new, slow-acting protamine zinc insulin very often failed to control glycosuria, particularly after meals, and that one or more supplementary doses of quick-acting, regular insulin were required for adequate control. The necessity of only one additional dose would have offered no great handicap. In many cases, however, two or three supplementary injections of ordinary insulin were required. Sindoni,<sup>13</sup> having observed that the slow-acting insulin was far inferior to the older product in the prevention of postprandial glycosuria, concluded that protamine insulin itself was inadequate for diabetic management, and should, therefore, be prescribed only as an aid to regular insulin. Obviously, an increased number of injections, instead of simplifying the life of the diabetic, actually makes it more complicated.

Another obstacle frequently encountered with the use of protamine zinc insulin was inferior control of the diabetes. This fault was inherent in the

- c. Two animals—tachycardia.
- d. Seven animals—ventricular fibrillation.
- e. Three animals—cardiac standstill.

The pathological changes to a great extent are predetermined by the underlying state of the heart and the trauma often acts as a precipitating or exciting cause. This fact can readily be illustrated by a list of the diagnoses in this series.

- Case 1. Contusion and hematoma of the myocardium and possibly pericardium.
- Case 2. Healed rheumatic endocarditis, contusion of the heart with moderate loss of function.
- Case 3. Contusion of the heart, nodal extra systoles, cardiac neurosis and effort syndrome.
- Case 4. Coronary thrombosis.
- Case 5. Luetic aortitis and myocarditis, aneurysm of the first portion of the aorta.
- Case 6. Luetic myocarditis and aortitis.
- Case 7. Myocarditis and first stage heart block, possible coronary thrombosis.
- Case 8. Chronic myocarditis and cardiac decompensation.
- Case 9. Coronary thrombosis and angina pectoris.
- Case 10. Chronic myocarditis, bundle branch block, loss of cardiac function.

Any type of chest trauma may focus the patient's attention on the heart and give rise to cardiac neurosis<sup>23</sup> or the so-called effort syndrome (see case 3).

Trauma: All the patients (except case 10) sustained a direct nonpenetrating trauma of the chest. This injury varied from the standpoint of quality, quantity and location. In some cases the offending force was applied to the precordium with external signs of trauma (cases 2, 4, 7 and 9). In the rest the injury was applied elsewhere on the chest and without external signs. These findings are in accord with the work of Bright and Beck<sup>7</sup> and the work done at the Medical Examiner's Office. How trauma acts on the chest to produce, precipitate or aggravate a heart lesion cannot always be explained satisfactorily. An enumeration of certain facts may help in understanding the mechanism involved:

1. The heart is not a firmly imbedded organ, but on the contrary is free and attached at its base by the large vessels. This anatomical fact allows the heart to be thrown violently against the bony structures of the chest or else torn at its attachment and thus damaged.

2. A hollow viscus which is distended and under pressure is more liable to be damaged by an injury than a similar organ which is relaxed. During systole the heart wall is under tension and trauma at that moment may rupture or damage this organ.

The shortcomings and dangerous potentialities of this most efficacious therapeutic agent offered, therefore, a challenge from the beginning of its use. Several means of avoiding difficulties had been suggested during the first two years of its trial. The original papers of Hagedorn<sup>1</sup> and the earlier papers of Root<sup>2</sup> which referred to this subject advocated the injection of protamine insulin late in the afternoon in order to obtain the maximum insulin absorption during the following day, when its effects would be matched with meals. With this type of administration the Danish originators advised that supper be the smallest meal of the day, and breakfast, the largest. In this country, however, established preference is for the small breakfast, the large supper. In America the earlier practice has been largely supplanted by the morning administration of protamine zinc insulin, both because the afternoon timing failed to prevent nocturnal insulin reactions and because, from the patient's standpoint, it was simpler to have the injection before leaving home in the morning. An added advantage of the morning injection is the fact that its effects are more uniform and better predictable on the smooth nocturnal blood sugar level i.e., when the patient is in the basal condition of rest, than upon the daytime levels, when exercise and other factors produce a widely fluctuating blood sugar content.

As an improved method of preventing nocturnal reactions from a morning dose of protamine insulin, Sprague<sup>3</sup> has suggested that a glass of milk and a few crackers be given before bedtime. We, as well as others, have found this measure valuable, though often inadequate. Rabinowitch has logically advised the use of six feedings a day in order to minimize tendencies to both glycosuria and reactions, but objection to such a regimen comes from the active diabetic, who usually finds the six-meal schedule burdensome. Joslin<sup>14</sup> has recommended that meals be spread further apart over the 12 hours, and that a trifling lunch of 5 to 15 gm. of carbohydrate, perhaps with a little protein, be added in the forenoon, afternoon and at bedtime. The principle demonstrated by this method particularly emphasized the desirability of dietary redistribution as a means of averting trouble, and focused our attention on the late feedings. The more experience we had with protamine zinc insulin, the greater we saw the necessity for large carbohydrate stores at night. We felt, therefore, that the most sustained protection against hypoglycemia would be afforded by a late supper that would be digested and absorbed slowly, while the patient sleeps.

#### THE FOUR-MEAL DIET

Since insulin dosage has always demanded the balancing of insulin action with proper dietary intake, and since, with protamine zinc insulin we were confronted with a new element, i.e., delayed action, it appeared mandatory to arrange a schedule so that absorbed food and slowed insulin action would meet in optimum relationship. We felt that because the greatest protamine insulin effect takes place at night, we should provide a more substan-

present in case 2. In the others the underlying condition dictated the resulting clinical picture.

The disability of any patient depends on the functional and structural damage, and occasionally, as in case 3, only a dysfunction results. The prognosis is an individual problem and depends on the type of damage.

### CONCLUSION

1. Direct nonpenetrating injuries of the chest are capable of producing cardiac damage.
2. This has been demonstrated at the bedside and in the laboratory.
3. The diagnosis of traumatic heart damage depends upon:
  - a. The awareness of this clinical possibility.
  - b. The history of a direct nonpenetrating injury to the chest.
  - c. A previous normal cardiovascular history.
  - d. The appearance of signs, symptoms or laboratory findings indicating heart damage and appearing in the great majority of the cases immediately after the injury and persisting thereafter.
4. In a fair percentage of patients there is usually a quiescent, underlying pathological process such as arteriosclerosis, hypertension, syphilis, blood dyscrasias, rheumatic infections, etc., which may dominate the clinical picture after such an injury.
5. Trauma may aggravate a known cardiac lesion.

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daily diets of our patients ranged from 166 to 300 gm.; while the total oxidizable glucose in the fourth meal alone was 32 to 53 gm.

A fairly representative 9:30 p.m. feeding consisted of the following foods or their equivalents:

Bread .....	1 slice
40 per cent cream .....	50 gm.
Milk .....	200 "
Eggs (or the equivalent, as meat or cheese) ..	2

Our more recent experience has indicated that the principle of providing an ample night feeding not infrequently requires further extension, particularly in severe diabetic patients. Thus, when one-fifth of the diet fails to produce perfect control, two-fifths, furnishing a total glucose value of 74 to 104 gm., may be more successful. In four of our cases (1, 6, 8 and 11) the necessity and effectiveness of such an extension are clearly emphasized.

#### CASE REPORTS

*Case 1.* R. P., a boy of 18, markedly underweight (81 lbs.-36 kg.), presenting severe diabetes of seven years' duration, was observed over a period of two years. During the control period in the hospital in October 1936, he had proved to be highly refractory to management with protamine insulin, because, while spilling 11 to 28 gm. of sugar in the urine during the day, he suffered on five occasions severe hypoglycemic reactions, marked by violent convulsions and loss of consciousness, during the night. An evening snack of 15 to 20 gm. of carbohydrate had proved inadequate for prevention of the nocturnal reactions.

Throughout the next year he was seen at intervals, and his food allowance was increased periodically to allow for growth. During 1937, he was receiving from 36 to 44 units of protamine zinc insulin. Glycosuria was only poorly controlled. Any attempt to raise the insulin dosage during this period resulted in violent hypoglycemic reactions which could not be eliminated by numerous modifications of the three-meal diet. When the glycosuria was under fair control, he suffered severe nocturnal insulin reactions and their aftermath of morning headaches. When the dose of protamine zinc insulin was reduced to obviate the appearance of hypoglycemic reactions marked glycosuria recurred.

*Four-meal regimen:* Because of the extremely erratic and generally unsatisfactory level of control it became apparent that a still greater supply of slowly absorbable glucose was needed at night, during the peak of protamine zinc insulin absorption. On August 18, 1937, we therefore began the use of a regular "fourth-meal," providing one-fifth of the total caloric intake at 9:30 p.m., instead of three standard meals, supplemented by a glass of milk at bedtime. The regimen was later modified to furnish fully one-third of the total daily calories (total available glucose 45 gm.) in the night feeding. With the institution of the new dietary arrangement management at once became simplified. With the modified diet an initial dose of 56 units of protamine zinc insulin was given in the morning. The continued presence of "loaded" sugar reactions in collections of all the urine samples demanded an increase in the dosage. The morning dosage of protamine zinc insulin was, therefore, increased gradually until at one time 100 units of protamine zinc insulin were attained, at which time all samples of urine in the 24-hour period became negative for sugar. Blood sugar levels which, at the beginning of treatment with the four-meal diet, ranged between 153 to

# THE TREATMENT OF DIABETES MELLITUS WITH A FOUR-MEAL DIET: A MEANS OF CIRCUM- VENTING CERTAIN DIFFICULTIES ARISING IN THE USE OF PROTAMINE ZINC INSULIN \*

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NEW therapeutic agents, like new servants, are apt to present their best sides first, and only upon longer acquaintance reveal the disagreeable traits which hinder their usefulness. Despite technical refinements and improvements in the uniformity and stability of the new insulin products, which culminated in the development of protamine zinc insulin, frequent failings of the slower acting insulins have become apparent with extended experience. Briefly, these failings were manifest in diurnal glycosuria, in the necessity for supplementary injections of regular insulin, in serious, even fatal, reactions, and often, in fact, in such erratic diabetic control as to force the abandonment of protamine zinc insulin in many cases where its aid would have been most welcome.

So manifold are the advantages of this new product, however, that, were it not for the annoying obstacles frequently encountered in its application, protamine zinc insulin would be today the most successful and popular therapeutic resource at the command of every physician who treats diabetes.

We present here our experience with a simple regimen through which we were able to circumvent the usual obstacles. Our method is essentially a departure from the standard three-meal diabetic diet schedule. We have initiated, instead, a modification of the diet so as to provide optimum glucose absorption in relation to the action of protamine zinc insulin. Since the distinctive physiologic property of protamine zinc insulin is its slow absorption, which produces the maximum depression of the blood sugar level some 10 to 24 hours after its injection, it seemed rational to make available an adequate supply of carbohydrate at the time of its greatest need (i.e., coincident with the lowest blood sugar levels). The essence of our program, therefore, was the provision of a liberal carbohydrate meal late in the evening, with the objective of furnishing a store of carbohydrate that would be fed into the blood stream during the night, *slowly and continuously*. This method, it will be demonstrated, stands in contradistinction to the ordinary practice of furnishing a bit of quickly absorbable glucose late in the evening as a precaution against nocturnal reactions.

We found that the four-meal procedure yielded smooth and relatively

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TABLE I

Case No.	Age	Sex	Dates of Observation on Each Regimen	Diet				Fourth Meal Gm.				Insulin Maintenance Dosage	Degrees of Glycosuria	Hypoglycemic Reactions	Time Required for De-sugarization	Remarks
				Carbohydrate, gm.	Protein, gm.	Fat, gm.	Total Glucose Value, gm.	Calories	C	P	F	Total Oxidizable Glucose, gm.				
1 (R. P.)	16	M.	On 3-meal Oct. 1936 to Aug. 1937	150	90	99	210	1850					Average 20-40 gm. daily	Frequent and severe with loss of consciousness. Gen. nocturnal	3 wks. in hospital	Had been receiving 15 gm. glucose as orange juice 10 a.m., 3 to 9 p.m. daily with 3-meal diet. Average fasting blood sugar levels 60 to 90 mg. while on 3-meal diet.
			On 4-meal Aug. 1937 to Apr. 1939	225	95	170	310	2810	75*	31	38	103	Less than 5 gm. usually 24 hr. sample sugar-free	None in 20 months	2 wks. in hospital	Diet had been increased to allow for growth and greater physical activity. At one time took 100 u. prot. zn. insulin for control without provoking reactions. Av. fasting blood sugar levels 100 to 130 mg. on 4-meal diet.
2 (K. G.)	57	F.	On 3-meal Jan. 1937 to Nov. 1937	250	70	90	299	2090					7-14 gm. daily	None	Never entirely sugar-free	Complained of hunger on 3 meals. Fasting blood sugar levels usually elevated (180 to 220 mg.).
			On 4-meal Nov. 1937 to Dec. 1938	....	....	same	....	....	40†	15	15	50	None or less than 5 gm. in 24 hr.	None	10 days in hospital	No longer hungry. Slow gain in weight. Maintained excellent control during out-patient attendance 1 year. Fasting blood sugars 86-95 mg. Coincidental hypertrophic arthritis. Periods of weight loss. Fasting sugar levels 100 to 160 mg.
3 (E. G.)	66	F.	On 3-meal Apr. 1937 to Mar. 1938	225	75	90	278	2010					"Loaded" 24 hr. specimen	Several early morning. Three severe nocturnal shocks	Never entirely sugar-free	Weight maintained Diabetic control well-maintained over 1 year. Fasting sugar levels 130 to 150 mg.
			On 4-meal Apr. 1938 to Apr. 1939	....	....	same	....	....	44	14	17	54	None or "sl. trace"	None in 12 months	5 days in hospital	

\* 1/3 of total allowance.

† Sl. less than 1/5.

delayed action of the newer product. The single morning dose of protamine zinc insulin has been found to maintain its action over a period of 24 to 72 hours, oxidizing little glucose within the first four to six hours, but exerting its peak effect (i.e., of depressing the blood sugar level) some 10 to 24 hours after administration. Sprague and his associates<sup>3</sup> at the Mayo Clinic, as well as Mosenthal,<sup>8</sup> and others have demonstrated that protamine insulin had little discernible effect upon the blood sugar level during the day of its injection, whereas it frequently produced hypoglycemia during the ensuing night. As a consequence, sugar was spilled during the day rather than at night. This is just contrary to what had happened with the administration of ordinary insulin in divided doses, with which daytime glycosuria was generally adequately controlled by each mealtime dose of insulin, while nocturnal glycosuria was not readily controlled for lack of available insulin action. Allen,<sup>4</sup> in 1936, indicated this contrariness of control with the new preparation. Since then most workers with diabetes have become familiar with the paradox of protamine action: *sugar spilling by day; hypoglycemic reactions by night*.<sup>4, 7, 10, 11</sup> If the dosage of protamine insulin were increased, hypoglycemic shocks were provoked; if it were reduced, glycosuria became aggravated.<sup>4, 7, 10, 11</sup> So difficult has the problem of diurnal hyperglycemia and glycosuria become that men who had previously considered any glycosuria as evidence of inadequate diabetic control became reconciled to some degree of it with the use of protamine insulin.<sup>3, 9</sup> Others have, indeed, given up the attempt to control difficult diabetics with the new preparation.<sup>10, 11</sup> Although the question of the possible injurious effect of transitory hyperglycemia and glycosuria is still unsettled, it is certainly most desirable to attain complete control, whenever that is possible.

By far the most objectionable feature encountered with the use of protamine zinc insulin was the danger of grave hypoglycemic reactions. Unlike the reactions from ordinary insulin, which came on rapidly after administration, most often during the day, and were quickly controlled by orange juice, the reactions from protamine insulin were insidious in onset, crept on subtly during the night, tended to be prolonged, severe, recurrent, and little or only temporarily influenced by the customary sip of glucose. The gravest peril of the protamine insulin reactions was the nocturnal occurrence of delirium and unconsciousness which have been known to go on unobservedly to sudden death.<sup>12</sup> So ominous were these potentialities of the newer insulin that they were the subject of an editorial warning in the *Journal of the American Medical Association*<sup>12</sup>—a timely warning, issued during the time of our greatest enthusiasm for this new and generally useful therapeutic agent. The *Journal* reviewed the evidence necessitating this notice and stressed the fact that protamine zinc insulin was not, as some had hoped, a foolproof substitute for the older preparation. The greater hazard of hypoglycemic shock with the use of protamine zinc insulin stood, indeed, as a cogent and valid deterrent to its wider clinical application.

TABLE I—Continued

Case No.	Age	Sex	Dates of Observation on Each Regimen	Diet					Insulin Maintenance Dosage	Degree of Glycosuria	Hypoglycemic Reactions	Time Required for De-sugarization	Remarks
				Carbohydrate, gm.	Protein, gm.	Fat, gm.	Total Glucose Value, gm.	Calories					
7 (R. F.)	57	F.	On 3-meal Mar. 1938 to Apr. 1938	175	75	88	223	1800	Prot. zinc insulin 35 u. +	13 to 25 gm.	Several severe nocturnal	Sugar not controlled	Entered hospital presenting severe glycosuria, acetoneuria. Arteriosclerotic. Blood sugar level 190 to 240 mg. Fasting blood sugar levels 90 to 140 mg. Gained weight.
			On 4-meal May 1938 to Apr. 1939	...	...	...	...	...	Prot. zinc insulin 35 u.	None	None	10 days in hospital	
8 (M. B.)	40	M.	On 3-meal (3 weeks)	(Approximately 2900)					Variable prot. zinc insulin + regular insulin trial	Severe 20 to 30 gm. in first few days of hospitalization	None	Not controlled prior to hospitalization	Entered hospital in severe state of acidosis. Loss of 40 lbs. (18 kg.) in 3 weeks prior to admission. Diplopia; pains in legs.
			On 4-meal July 1938 to Mar. 1939	200	75	190	260	2800	Prot. zinc insulin only 32 u.	None	None	10 days in hospital	Very simply controlled. 4-meal diet used from start. Blood sugar levels 92 to 113 mg. Returned to hard physical labor and maintained weight and strength.
9 (R. L.)	46	F.	On 3-meal May 1936 to Aug. 1938	160	70	115	208	1950	Prot. zinc insulin 10 u.	Gen. "Loaded"	None	Never quite sugar-free	Diabetic out-patient. Had lost 40 lbs. (18 kg.) in weight in first 2 yrs. of illness. Complained frequently of hunger 1 hr. after meals.
			On 4-meal Aug. 1938 to Apr. 1939	...	...	...	...	...	Prot. zinc insulin 6 u.	None or faint trace	None	3 wks. dispens.	Gaining weight. Blood sugar levels 144 to 170 mg.

§ 2/5 of diet.

tial part of the diet at night. We sought, also, to take advantage of the well established principle that the diabetic patient tends naturally to be worse in the morning, better at noon, and best of all in the evening. Why not, then, furnish an ample meal at the time of greatest carbohydrate tolerance as well as of maximum protamine insulin action? To be most effective, a meal intended to meet the peak action of protamine zinc insulin during the night must perforce be: (1) adequate in carbohydrate content; (2) slowly absorbed so as to feed glucose continuously into the blood stream over a prolonged period; and (3) eaten late enough to be effective throughout the night.

From our previous experience we had found that 5 to 15 grams of carbohydrate, as advocated, were often entirely inadequate to control nocturnal reactions. We had observed several times that although the night snack did control one reaction, it did not prevent the recurrence of reactions later in the night. Behind this failure was the fact that the glass of orange juice or the glass of milk was too rapidly absorbed, too quickly spent. Inadequate protection resulted. These views were well crystallized, in our experience, with the use of protamine zinc insulin by a juvenile patient with rather severe diabetes (case 1), who had for some time impressed us with the necessity of furnishing larger and larger snacks of the diet in the evenings in order to protect him against the violent and recurrent insulin reactions to which he had been subject. Largely on empiric grounds we developed the practice of furnishing one-fifth of his total daily allowance of food in a night feeding. We favored foods in this meal that would be digested and absorbed slowly, yielding glucose not only from the starch, but also from the protein and fat in foods such as eggs, cream and butter. We felt that 9:30 or 10 p.m. was the best time for the fourth meal, inasmuch as that was over four hours after the usual dinner and still more than an hour before bedtime.

With these clinical impressions as a guide, we started on August 18, 1937 to prescribe a four-meal regimen with a *liberal night feeding* for patients who were taking protamine zinc insulin. The total diet prescriptions were the same, in general, as those upon which the patients had been previously maintained. These were calculated to supply the individual's caloric needs. Formerly these patients had taken three meals of approximately equal portions (or of  $1/5$ ,  $2/5$  and  $2/5$  respectively, according to the individual patient's tastes).

The new four-meal diets were divided as follows:

- $1/5$  of the total caloric intake at 8 a.m.
- $1/5$  at noon
- $2/5$  at 5 p.m.
- $1/5$  at 9:30 p.m.

The prescribed carbohydrate content was, on an average, over 180 gm. The total available glucose from the carbohydrate, protein and fat in the

TABLE I—Continued

Case No.	Age	Sex	Dates of Observation on Each Regimen	Diet					Fourth Meal Gm.	Insulin Maintenance Dosage	Degree of Glycosuria	Hypoglycemic Reactions	Time Required for De-sugarization	Remarks
				Carbohydrate, gm.	Protein, gm.	Fat, gm.	Total Glucose Value, gm.	Calories						
13 (M. L.)	56	F.	On 3-meal June 1938 to Aug. 1938	150	60	18	187	1000	C	—	"Loaded" 24 hr. specimen	None	—	Obese, but had lost 40 lbs. (18 kg.) within two months of onset of diabetes. This case the only low caloric diet in series. Blood sugar levels 230 to 250 mg. in a.m.
				...	...	...	...	...	P	—				
				...	...	...	...	...	T	—				
14 (N. N.)	42	M.	On 4-meal Aug. 1938 to Apr. 1939	...	...	...	...	30	12	3.5	37	Prot. zinc insulin 20 u.	6 days in hospital	Acetone and diacetic acid negative. Safety on low caloric, 4-meal diet. Fasting blood sugar levels 162 mg. Untreated diabetes for 1 yr., complicated by coronary-sclerosis. (Case included to illustrate value of starting control with 4-meal regimen.)
				...	...	...	...	...	...	...	15 gm. in 24 hrs. on admission	—	—	
				...	...	...	...	...	...	...	None	None in 9 months	9 days in hospital	
			On 4-meal Aug. 1938 to Apr. 1939	195	80	95	251	1950	39	16	19	49	Prot. zinc insulin 35 u.	Fasting blood sugars 100 to 130 mg. Rapid control of diabetes with 4-meals. Safety (no reactions) in presence of coronary sclerosis through use of protective fourth meal.

295 mg. per 100 c.c. of blood, at various times of the day, descended to levels of between 70 to 111 mg., with complete control of the diabetes, within two weeks.

The most instructive feature of this case was the fact that the large dose of protamine zinc insulin required for control was, with the four-meal diet, tolerated without provoking any insulin reactions. The smoothness and rapidity with which control of the diabetes was achieved with the new regimen was in striking contrast to our experience in the treatment of this boy previously with the more usual forms of diabetic management. At the time of writing he has gained considerable carbohydrate tolerance and is being maintained in perfect diabetic control with 80 units of protamine zinc insulin daily.

*Case 2.* K. G., a white female, 57 years old, weighing 140 lbs. (63 kg.) had been treated for diabetes in the outpatient clinic for two years. This was the second case to demonstrate the value of a fourth meal. She was admitted to the Montefiore Hospital for the treatment of acute lumbosacral sprain November 8, 1937. During her stay she continued her usual three-meal diabetic diet (see chart), with which she received 40 units of protamine zinc insulin. Glycosuria (7-14 gm. sugar per 24-hour specimen) occurred during the first 10 days, while the fasting blood sugar level ranged within normal limits. The protamine zinc insulin dosage was gradually increased to 58 units, and a slice of bread with a glass of milk from the noon feeding was ordered for 9:30 p.m. The glycosuria diminished to 5 gm. daily, most of the sugar loss taking place in the afternoon and evening. The fasting blood sugar remained at 107 mg. Later the original dietary prescription was further rearranged so as to furnish one-fifth of the total daily calories (total available glucose 58 gm.) in the 9:30 p.m. feeding. During the following week all of the 24-hour samples tested negative for sugar, and the fasting blood sugar levels remained normal. Since her discharge from the hospital she has continued on the four-meal regimen and has reported regularly to the outpatient clinic for over a year. She has remained controlled, has maintained her weight, has required smaller doses of protamine zinc insulin, being controlled on 40 units daily.

*Case 3.* Mrs. E. G., aged 66, had been under regular observation at the diabetic clinic of the Montefiore Hospital for three years prior to her admission February 19, 1938, for treatment of hypertrophic arthritis of one knee. In the clinic she had almost constantly a moderate degree of glycosuria concurrent with fasting blood sugar levels of 100-110 mg. per 100 c.c. Upon admission she was maintained on her customary diet of carbohydrate 225 gm., protein 75 gm., fat 90 gm., divided about equally among three meals. Her usual dosage of 50 units of protamine zinc insulin daily, supplemented by 20 units of regular insulin at 8 a.m., was also prescribed. Because of an insulin reaction on the morning of February 21, the regular insulin was discontinued. For several days she presented a mild degree of glycosuria (1 gm. in 24 hours), predominantly in the 6 p.m. sample. On February 23, blood sugar determinations at 8 a.m., 11 a.m., and 4 p.m. were 101, 165 and 102 mg. per 100 c.c. of blood, respectively. At 2 a.m. of the following night she suffered an insulin reaction marked by tremor and profuse sweating. She left the hospital March 4, 1938.

Because of another severe attack of arthritis she was readmitted to the hospital March 30, 1938. The daily diet prescription was left unaltered, except that the food was distributed at that time into four meals, allowing one-fifth of the total dietary intake at 9:30 p.m. This redistribution was made in the desire to circumvent the recurrence of insidious insulin shocks in a woman of her age. With the modified regimen and 45 units of protamine zinc insulin no glycosuria appeared in the 24-hour specimen during the next two weeks. On only two occasions were there traces of sugar in single, afternoon voided specimens. The fasting blood sugar on April 14 was 136 mg. At no time during this hospital stay did any insulin reactions occur. She was discharged April 14, 1938, and has reported periodically to the outpatient

fat, divided into three nearly equal meals, except for 10 gm. of carbohydrate which were furnished at 9 p.m. With this diet he required 40 units of protamine zinc insulin, supplemented by a morning dose of 15 units of soluble insulin. Whereas the fasting blood sugars were normal on this regimen, glycosuria was severe, ranging from 8 to 30 gm. daily. In spite of the glycosuria occasional reactions appeared. When the carbohydrate allowance was gradually reduced by 40 gm. and soluble insulin omitted considerable diurnal glycosuria still persisted.

We felt that since hypoglycemic reactions might prove disastrous to a person of his age and myocardial status, they should be avoided, if at all possible. On July 1, 1938, his regular dietary allowance was redistributed into a four-meal regimen which provided the greatest supply of food, i.e., fully two-fifths of the total allowance in the 9 p.m. feeding. The total glucose value of the night feeding was 45 gm. The protamine zinc insulin dosage of 40 units daily was maintained. During the following 20 days practically all urine specimens tested negative for sugar, while the fasting blood sugar level varied from 85–163 mg. By July 22, 1938, the patient required only 35 units of protamine insulin for control. (Subsequently, the gangrene of the foot spread, the patient refused operation, and died August 7, 1938.)

*Case 7.* Mrs. R. F., aged 57, was referred for control of recently discovered diabetes. She entered the hospital April 20, 1938, presenting marked glycosuria, acetonuria, and a fasting blood sugar level of 200 mg. per 100 c.c. of blood. Her diet consisted of carbohydrate 175 gm., protein 75 gm., fat 88 gm., in three meals. With this diet she required 35 units of protamine zinc insulin for partial control of glycosuria. With this dosage, or even less, she suffered several nocturnal insulin reactions. The diet was, therefore, rearranged into four meals, providing a total glucose allowance of 42 gm. at 9:30 p.m. daily. The protamine zinc insulin dosage remained at 35 units. Subsequent to this change she was free from reactions. She was discharged from the hospital May 13, 1938, and was advised to continue on the four-meal regimen. In the ensuing nine months she has had no reactions, has gained 10 lbs. (4.5 kg.) in weight, has had no glycosuria, and her fasting blood sugars have remained at normal levels.

This case well illustrates what often occurs in the attempted management of a diabetic patient with protamine insulin and the use of a standard three-meal diet i.e., just when the glycosuria is beginning to disappear hypoglycemic reactions set in. The dual rôle of the fourth meal, other conditions remaining the same, is well demonstrated in this case.

*Case 8.* M. B., aged 40, a steel worker engaged in heavy physical work, complained of pains in the legs, difficulty with vision, and loss of 40 lbs. (18 kg.) in weight within the three weeks prior to his examination, and was found to be suffering from acute, severe diabetes. He entered the Montefiore Hospital July 10, 1938 in a state of severe acidosis, for the control of which protamine zinc insulin plus soluble insulin was used. The prescribed diet contained 200 gm. carbohydrates, 75 gm. protein, 190 gm. of fat, divided into four meals. After four days of treatment there was still an excretion of 12 gm. of sugar in the urine for a 24-hour period, but the fasting blood sugar fell to 81 mg. The night (9 p.m.) allowance of food was, therefore, increased from one-fifth to two-fifths of the day's total. There was no need for supplementary regular insulin within two days after this change, a morning dose of 45 units of protamine zinc insulin alone sufficing for adequate control. The urine specimens for six days prior to discharge were uniformly sugar-free, while the fasting blood sugar levels ranged from 113 to 134 mg. Within 16 days of admission the patient was discharged from the hospital entirely sugar-free. During the following nine months, back at his regular hard work, he required, with a continued four-meal regimen, only 32 units of protamine zinc insulin to maintain uniformly perfect control of his diabetes.

TABLE I—Continued

Case No.	Age	Sex	Dates of Observation on Each Regimen	Diet					Insulin Maintenance Dosage	Degree of Glycosuria	Hypoglycemic Reactions	Time Required for De-sugarization	Remarks
				Carbohydrate, gm.	Protein, gm.	Fat, gm.	Total Glucose Value, gm.	Calories					
4 (R. M.)	42	F.	On 3-meal Apr. 1936 to May 1938	175	75	120	232	2080	50 to 80 u. daily Prot. zinc insulin	"Loaded" 24 hr. specimen	None	Never entirely sugar-free	Severe diabetes; loss of weight. Received also 15 gm. carbohydrate as milk every evening, in addition to 3 meals. Low fasting blood sugars 94 to 97 mg.
5 (S. M.)	68	F.	On 4-meal May 1938 to Apr. 1939	160	70	111	211	1919	Prot. zinc insulin 40 u.	None or faint-trace	None	1 week in hospital	Operation for cervical polyps. Controlled with individual doses soluble insulin during post-operative days only. Four meal diet resumed after 5 days. Weight gained.
6 (W. M.)	72	M.	On 3-meal Sept. 1937 to Apr. 1938	200	65	100	248	1960	Prot. zinc insulin 40 u.	Gen. "Loaded" 24 hr. specimen 4 to 8.5 gm.	None	Not completely in 8 months	Diabetic and arthritic out-patient. Wass. ++++. Elderly and arteriosclerotic. Blood sugar levels av. 150 to 200 mg.
6 (W. M.)	72	M.	On 4-meal Apr. 1938 to Apr. 1939	...	...	same	e. . . . .	46	Prot. zinc insulin 15 u.	Consistently sugar-free 24 hr. samples	None	9 days hospital	Because of improvement under anti-arthritic therapy, became more active physically; required less insulin. Gained weight. Fasting blood sugars usually 140 to 150 mg.
6 (W. M.)	72	M.	On 3-meal June 1938 to June 1938	195	65	106	243	1994	Prot. zinc insulin 40 u. + soluble insulin 15 u.	8 to 30 gm. daily	Several	Not sugar-free	Senile; diabetes of 3 yrs. duration. Auricular fibrillation (recent). Gangrenous ulcer of foot (recent). Received orange juice 9 p.m. (10 gm. carb.).
6 (W. M.)	72	M.	On 4-meal July 1938 to Aug. 1938	150	70	100	200	1780	Prot. zinc insulin only 40 u.	Almost entirely sugar-free 20 days	None	5 days in hospital	During hosp. control fasting. Blood sugar levels 85 to 163 mg. Spread of gangrene; patient refused operation. Died.

‡ 2/5 of diet.



the same dosage. This occurs because each meal is no longer oxidized by the direct, immediate action of a meal-time dose of soluble insulin, but by the delayed and variable action of protamine zinc insulin given in the morning. Previously, this eventuality would have been met by adding supplementary regular insulin at each meal. The simpler alternative, illustrated in this case, is to lop off some of the food from breakfast, lunch and dinner, in order to provide a night meal that is readily utilized at the height of protamine zinc insulin action. We feel that without the four-meal diet, providing a protective night meal, this patient might not have tolerated, without serious reactions, the 60 units of protamine zinc insulin required for control.

*Case 12.* L. M., 67 year old colored female, has attended the diabetic clinic since 1935. During the period of management with soluble insulin she had received 15-0-15 units, but presented frequent periods of glycosuria (generally nocturnal), and fasting blood sugar levels ranging from 178 to 295 mg. From November 1937 to July 1938 she received an 1800 calorie, three-meal diet, with 20 to 30 units of protamine zinc insulin. Upon this regimen, while she spilled less sugar than formerly (generally in the afternoon and evening specimens), she maintained a high fasting blood sugar level (260 mg.). On August 17, 1938, she was ordered a diet of higher caloric value (2100 calories), divided, however, into four meals. She was maintained on 30 units of protamine zinc insulin daily. Within two weeks the patient achieved the best diabetic control that she had presented in three years, and has remained controlled until the time of writing.

This case illustrates the difference in problems offered by the old insulin and the new. In the days when quick-acting, regular insulin was administered with meals, sugar was controlled by day, spilled by night. With slow-acting protamine zinc insulin sugar was spilled during the day, since the new insulin did not attain its maximum effect until night. In view of this peculiarity of the newer insulin, a fourth meal was given at night and was efficiently utilized. This change resulted in the best diabetic control that this patient had enjoyed in three years of treatment.

*Case 13.* M. L., a 56-year-old female, was admitted to the Montefiore Hospital because of a recently discovered diabetes of approximately two months' duration. She was obese, but stated that she had dropped in weight from 245 pounds (111 kg.) to 203 pounds (92 kg.) coincident with the onset of symptoms of diabetes two months before. On a 1000 calorie diet, containing carbohydrate 150 gm., protein 60 gm., and fat 18 gm., divided into four meals, and with 20 units of protamine zinc insulin daily, the urine specimens which had been loaded with sugar for the first three days, became negative, except for one 24-hour period, four days before discharge, when 6.4 gm. of sugar were spilled. Thereafter, 24-hour collections of urine remained consistently sugar-free. Two fasting blood sugar determinations taken prior to the four-meal dietary plan were 238 and 254 mg. per 100 c.c. of blood, respectively, while those taken after the change were 162, and, on the day of dismissal, 129 mg. Perfect diabetic control having been established, the patient was discharged within one week after admission to the hospital, and has remained sugar-free since.

*Case 14.* N. N., a salesman, 42 years of age, was admitted to the Montefiore Hospital for control of previously untreated diabetes of one year's duration. He also presented a history of one attack of severe angina pectoris three years previously, attributable to coronary sclerosis. On admission, he spilled 15 gm. of sugar in a 24-hour collection of urine, and his fasting blood sugar level was 250 mg. per 100 c.c. of blood. A diet of 1950 calories, containing carbohydrate 195 gm., protein 80 gm., and fat 95 gm., divided into four meals, was prescribed. One-fifth of the daily food allowance was given at 9:30 p.m. With the daily administration of 35 units of protamine zinc insulin the 24-hour specimens of urine became sugar-free and the fasting blood sugar reached a level of 129 mg. per 100 c.c. of blood. Control of the diabetes was attained on the ninth day of hospitalization. At no time have insulin

TABLE I—Continued

Case No.	Age	Sex	Dates of Observation on Each Regimen	Diet					Fourth Meal Gm.				Insulin Maintenance Dosage	Degree of Glycosuria	Hypoglycemic Reactions	Time Required for De-sugarization	Remarks
				Carbohydrate, gm.	Protein, gm.	Fat, gm.	Total Glucose Value, gm.	Calories	C	F	Total Oxidizable Glucose, gm.						
10 (M. M.)	66	F.	On 3-meal May 1937 to Aug. 1938	200	65	100	247	1960					Prot. zinc insulin 24 to 32 u.	"Trace" to "Loaded"	None	—	Diabetic out-patient. Poor coöperation because of hunger between meals. Fasting blood sugars range 185 to 233 mg.
			On 4-meal Aug. 1938 to Apr. 1939	...	...	same	...	40	13	20	49	Prot. zinc insulin 25 u.	None or o.c. "trace"	None	4 wks. dispens.	Satiety with diet; better coöperation. Fasting sugar levels 130 to 150 mg.	
11 (F. S.)	50	F.	On 3-meal 1933 to July 1938	140	55	60	176	1320					Soluble insulin 20-0-20 u. Later prot. zinc insulin 40 u.	"Trace" to "Loaded" 24 hr. specimen	None	—	Diabetic out-patient. Blood sugar levels 295 to 350 mg. Attempt at abrupt change from soluble to prot. insulin provoked nausea, anorexia, loss of weight and increased glycosuria.
			On 4-meal July 1938 to Apr. 1939	160	65	60	204	1440	32	13	12	40	Prot. zinc insulin 50 u.	None	None	5 wks. dispens.	Gaining weight. Fasting blood sugar levels 95 to 160 mg.
12 (L. M.)	67	F.	On 3-meal 1935 to July 1938	120	60	120	166	1800					Soluble insulin 15-0-15 u. Later prot. zinc insulin 20 u.	Traces to "Loaded" 24 hr. specimen	None	—	Diabetic out-patient; markedly under weight; arteriosclerotic; chronic bronchitis; hunger a frequent complaint. Fasting blood sugar range 230 to 275 mg.
			On 4-meal July 1938 to Apr. 1939	...	...	same	...	24	12	24	33	Prot. zinc insulin 30 u.	None or occ. trace	None (10 months)	6 wks. dispens.	No reaction in spite of increased protamine insulin dosage required for control, although patient is markedly arteriosclerotic. Gaining weight. Fasting blood sugars 160 to 180 mg. Satiety with 4 meals.	

dren, a lower level of control resulted from the use of protamine zinc insulin. We have found the reverse to be true with the use of the four-meal diet in adults. Not only was the blood sugar in these controlled cases maintained at lower, more normal levels than before, but there was an absence of the wide fluctuations which had previously been observed with the standard three-meal program. With the four-meal regimen we no longer face the problem of glycosuria by day, hypoglycemia by night.

Contrary to the experience of Mosenthal,<sup>8</sup> Ralli,<sup>10</sup> and others who found that patients requiring over 50 units of insulin daily were difficult or impossible to control with the use of the new insulin, our experience with several cases that had previously required 50 to 80 units of protamine zinc insulin daily was that these severe diabetics achieved and maintained excellent diabetic control with the four-meal regimen and a single daily injection of protamine zinc insulin (cases 1, 2, 3, 4). Although our cases were not those of juvenile diabetics, it is possible that the principle of this regimen might be applicable with a similar degree of success in juveniles also. Diabetic control, once achieved, has been maintained over periods varying from six months (minimum) to over one year of observation. It is our opinion that a higher level of control, rather than the opposite, has been made possible by the use of protamine insulin, if combined with the four-meal diet.

The greatest benefit derived from the new regimen was the effective prevention of nocturnal insulin reactions through the use of the *protective fourth meal*. It will be observed from the chart that several patients (cases 1, 3, 6, 7) who had previously suffered repeated hypoglycemic reactions while on a three-meal regimen, or a three-meal regimen with a snack (15 gm. carbohydrate) at bedtime, suffered none on the four-meal regimen which furnished 30 to 50 gm. of carbohydrate at 9:30 p.m. This was true even of our youngest, most severe diabetic, who required 100 units of protamine zinc insulin daily. The nocturnal and fasting blood sugar levels were, on a whole, above the hypoglycemic levels that had previously been encountered with the use of protamine insulin. Even the patients who received over 40 units daily remained free of reactions. Significantly, the patient taking at one time 100 units (case 1) suffered not a single reaction while on the four-meal diet. Since smaller doses of protamine zinc insulin were generally necessary after adoption of the new dietary habit, less hazard of hypoglycemia existed. Since the use of supplementary soluble insulin had been made unnecessary the danger of diurnal shocks was likewise minimized. It is significant that even in those cases where the dietary formula and the protamine zinc insulin dosage remained unchanged, redistribution of the food to provide a night meal at the height of the delayed protamine insulin action sufficed to prevent violent nocturnal reactions.

Because one-fifth or even two-fifths of the total diet was furnished at night, even elderly, arteriosclerotic patients were able to utilize protamine insulin without fear of reactions or the risk of a fatality (cases 3, 5, 6,

department since. Continuing the four-meal regimen and the use of 40 units of protamine zinc insulin daily, the patient has remained under good diabetic control and free from insulin reactions. The excellent control achieved with the four-meal regimen is a striking contrast to the former control period (with three meals), during which diurnal glycosuria alternated with frequent nocturnal reactions.

*Case 4.* Mrs. R. M., a severe diabetic, aged 42 years, had been treated in the outpatient clinic for two years. Prior to 1938 she had required 80 units of regular insulin with a 2080 calorie, three-meal diet for control. In February 1938, she was placed on protamine zinc insulin, requiring 80 units every morning. In the evenings, at 9 p.m., she received 200 gm. of milk (carbohydrate value 15 gm.) from her dietary allowance. Since her transfer to protamine zinc insulin, she had presented, almost daily, moderate to severe glycosuria, while, at the same time, her morning blood sugars were low (94–97 mg. per 100 c.c.). On May 13, 1938 she was admitted to the hospital to undergo vaginal hysterectomy for uterine polyps. At this time a 1920 calorie diet was prescribed, consisting of carbohydrate 160 gm., protein 70 gm., fat 111 gm., divided into three meals and a night allowance of milk, as described. She received 50 units of protamine zinc insulin daily. Glycosuria persisted, while the fasting blood sugar levels were low. The diet formula was, therefore, rearranged into four meals, furnishing one-fifth of the food at 9:30 p.m. (total glucose value 45 gm.), while the protamine zinc insulin dosage remained unchanged. Within several days the urine became entirely sugar-free and remained so.

On June 4, 1938, the patient was operated upon, under gas anesthesia. During the immediate postoperative period (five days) soluble insulin only was used in doses indicated by the degree of glycosuria. By June 10, when the patient was again able to take her full four-meal diet, the use of protamine zinc insulin was resumed and was gradually reduced to 35 units daily, which fully controlled the glycosuria and kept the fasting blood sugar at a normal level. For the remaining period of hospitalization all samples of urine were negative for sugar. She was discharged June 16, 1938. Periodic check-up during the next eight months indicated that the patient remained well controlled, maintained her weight, was using only half the dose of protamine zinc insulin (40 U.) that had been required previously to maintain a normal blood sugar level with the same caloric intake.

*Case 5.* S. M., a colored female, aged 68, diabetic and arthritic, was observed for years in the outpatient clinic. She was maintained on a 1960 calorie diet, together with 40 units of protamine zinc insulin daily. Review of her record for the past eight months showed that as a rule she presented marked glycosuria at each clinic visit. She was admitted into the hospital April 9, 1938. Her dietary prescription was modified into a four-meal distribution, the total glucose value of the 9:30 p.m. feeding being 46 gm. The urine became regularly sugar-free when a daily morning dose of 22 units of protamine zinc insulin was attained, and she remained aglycosuric for the remaining 20 days in the hospital; the fasting blood sugar level was maintained at approximately 160 mg. She was discharged from the hospital May 20, 1938. Under appropriate therapy, her arthritic symptoms were relieved and she became more active physically, consequently requiring less insulin during the eight months following her discharge. At the time of writing she required only 15 units of protamine zinc insulin daily, was free of glycosuria, and the fasting blood sugar level was 145 mg. per 100 c.c. of blood. Most apparent benefit of the smaller, more efficiently utilized insulin dosage was the minimal risk of provoking dangerous insulin reactions in this elderly patient.

*Case 6.* W. McC., male, aged 72, was admitted into the Montefiore Hospital June 24, 1938, with diabetes of three years' duration as well as a gangrenous, infected ulcer of the foot, and auricular fibrillation, both of recent onset. Upon admission he was continued on his former diet of 195 gm. carbohydrate, 65 gm. protein, and 106 gm.

to sacrifice the exactitude with which we could previously balance a given amount of carbohydrate in an individual meal with a suitable dose of soluble insulin. But this disadvantage is more than offset by the many conveniences offered by the newer product. Protamine insulin, properly used, furnishes a physiologic reservoir of insulin in the body. Up to the present our command over this reservoir has not been as complete as we might wish. It would undoubtedly be highly desirable to have a type of insulin, the action of which would be uniform and sufficiently prolonged to oxidize glucose throughout the day. Until such a product is perfected, however, we must resort to several other expedients in order to obtain safe, yet effectual, results with the use of protamine zinc insulin.

The trouble with protamine zinc insulin has been that a dose just sufficient to control diurnal glycosuria frequently proved inadequate to control hyperglycemia. If that dosage was increased, reactions occurred; if it was decreased, supplementary soluble insulin was required to control spilling of sugar during the day. Aside from the inconvenience, a constant danger is present with the use of added doses of soluble insulin, namely, that the patient is apt to get a double action of insulin—first, from the quick acting soluble dose; second, from the slowly liberated protamine insulin—at the great risk of reactions. Supplementing the diet with snacks between meals for the prevention of such diurnal reactions is a complicated, and frequently unsatisfactory expedient. We have not found it necessary to use feedings between meals, yet we encounter no diurnal reactions with the use of the four-meal regimen. In present diabetic management, as in standard management of peptic ulcer, frequent feedings are demanded; the advantageous distribution of these feedings is of the greater importance in diabetes.

Our suggestion, simply stated, is this: since, with a single injection of protamine insulin, we can no longer place insulin action precisely at those points around the clock where the food is, we can, with a high factor of safety, place food where the greatest insulin action is.

### CONCLUSIONS

In order to obtain the maximum efficiency with the use of protamine zinc insulin, a four-meal regimen of diabetic management, including a liberal food allowance late in the evening, was instituted. Whereas the daily dietary formulae were those common in modern diabetic practice, including high carbohydrate diets, the *distribution* of food was such as to provide the greater absorption of glucose at the time of the greatest absorption of protamine zinc insulin.

A series of 14 controlled cases is presented, illustrating the basis of our present use of the four-meal diabetic regimen, from which we conclude:

1. The four-meal regimen affords the utmost simplicity of diabetic treatment. A single daily injection of protamine zinc insulin suffices for

From previous experience we feel that with the standard three-meal regimen and protamine insulin the management of this case would have been one fraught with many difficulties i.e., persistent glycosuria, reactions, the necessity of repeated supplementary injections of regular insulin in addition to the protamine zinc insulin, recourse to supplementary feedings, and a longer period of hospitalization until control was finally achieved. With the four-meal regimen as a recourse, the zig-zag course of constantly varying food and insulin prescriptions previously demanded in such cases appears to have been obviated.

*Case 9.* Mrs. R. L., aged 46, observed in the outpatient clinic, had lost considerable weight in the past two years, coincident with the onset of diabetes. With a 1930 calorie diet of three meals, and a matutinal dose of 10 units of protamine zinc insulin, the fasting blood sugar level dropped to 147–160 mg. per 100 c.c. of blood. She presented considerable glycosuria, however, especially in the afternoon and evening specimens. She was troubled, besides, by hunger one hour or so after lunch, and more frequently after supper. On August 1, 1938 a four-meal division of her previous diet was instituted, furnishing one-fifth of the calories at 9:30 p.m. The protamine zinc insulin dosage was unchanged. Since this alteration, the 24-hour specimens of urine have become entirely sugar-free. Exceptionally, a trace of sugar appeared in single afternoon samples. She has no longer been troubled with hunger, has been content with her feedings, and has gained four lbs. (1.8 kg.) on her new regimen. At the time of writing her diabetes is perfectly controlled with only 6 units of protamine zinc insulin.

*Case 10.* Mrs. M. M., an ambulatory diabetic patient in our clinic, aged 66, had been under observation for 16 months, during which period she was taking a 1960 calorie, three-meal diet, together with 24 to 32 units of protamine zinc insulin daily. The fasting blood sugar levels had been in the proximity of 200 mg. throughout this period, while the 24-hour urine sample almost invariably showed sugar in amounts varying from traces to loaded specimens. This patient, we knew, frequently deviated from her diet by nibbling between meals. She has been observed periodically for a period of nine months since she started on the four-meal diet, has been observed to be more content with the prescribed feedings, and hence more coöperative. There has been considerable improvement in the control of the diabetes, as well as in the patient's morale. The urine has remained consistently sugar-free, the fasting blood sugar levels have dropped to 130–150 mg.; the amount of protamine insulin required has been 30 units.

*Case 11.* Mrs. F. S., 50 years old, has attended the diabetic clinic since 1933. In previous years, with a 1320 calorie diet, she had required soluble insulin in the dosage of 20–0–20 units for moderately good control. An attempt early in 1938 to change from regular insulin to 40 units of protamine zinc insulin while on a three-meal diet resulted in a break of control. She lost almost 10 pounds within two weeks and spilled considerable sugar. On July 10, 1938, the patient was placed on a four-meal regimen (1440 calories) of carbohydrate 160 gm., protein 65 gm., fat 60 gm., together with an initial dose of 35 units of protamine zinc insulin daily. Marked glycosuria persisted. The dosage was gradually raised to 60 units of protamine zinc insulin and was well tolerated without reactions.

Traces of sugar, at first present after the change, disappeared within several weeks. Periodic check-up over a period of nine months after the change to the four-meal regimen revealed no sugar in the 24-hour specimens of urine, fasting blood sugars of 88 and 90 mg. per 100 c.c. of blood, and a gain in weight of three lbs. (1.5 kg.). At the time of writing, the patient required only 50 units of protamine zinc insulin daily for control.

A period of poor control, such as is represented in this case, is frequently encountered upon making the change from soluble insulin to protamine zinc insulin of

# ROENTGEN TREATMENT OF THE ADRENAL GLANDS IN ANGINA PECTORIS (ONE HUNDRED CASES) \*

By W. RAAB, *Burlington, Vermont*

## A NEW THEORY OF ANGINA PECTORIS

THE typical occasions on which angina pectoris complaints occur, namely physical exertion, cold temperature and psychic emotion are physiologically connected with discharges of adrenalin from the suprarenal medulla as has been demonstrated in animals by Cannon <sup>1</sup> and his co-workers, and in man by Meythaler and Wossidlo.<sup>2</sup>

The specific effect of adrenalin upon the metabolism of the heart muscle consists essentially of a marked increase in local oxygen consumption (Barcroft and Dixon,<sup>3</sup> Evans and Ogawa,<sup>4</sup> Gremels,<sup>5</sup> Rein,<sup>6</sup> etc.). This exceeds by far the intensity of oxidation which is required to meet the needs of the increased hemodynamic action and does not coincide with it (Gollwitzer-Meier, Kramer and Krüger <sup>7</sup>).

According to the same authors the increase of myocardial oxygen consumption following the administration of adrenalin is much greater than the simultaneous increase of coronary blood flow in the denervated heart of the dog:

	Increase of O <sub>2</sub> -consumption of the heart muscle	Increase of coronary blood flow
30 sec. after 0.01 mg. adrenalin ....	+ 251%	+ 46%
45 sec. after 0.01 mg. adrenalin ....	+ 190%	+ 77%

In the innervated heart similar reactions take place, although to a minor degree. Accumulation of lactic acid in the heart muscle due to shortage of oxygen under the influence of adrenalin has been observed by Weicker,<sup>8</sup> Gottdenker and de Marchi,<sup>9</sup> etc.; histological myocardial changes of the anoxia type have been described by Franz,<sup>10</sup> Veith <sup>61</sup> and others after injections of adrenalin.

The explanation of angina pectoris sensations as being caused by a shortage of oxygen and formation of anoxybiotic acid metabolites within the heart muscle due to "coronary insufficiency" (Keefer and Resnik <sup>11</sup> and others) is generally accepted and does not require any further comment.

Gollwitzer-Meier <sup>12</sup> in a recent survey concerning the production of energy by the mammalian heart makes the following remark on the effect of adrenalin: "This sudden increase in oxygen consumption must lead to the danger of tissue anoxia if the increase of coronary blood flow is not an adequate one." It is evident that this will be the case in the presence of arteriosclerotic changes in the walls of the coronary arteries. In considera-

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reactions, particularly dangerous in the presence of coronary sclerosis, occurred. Diabetic control has been well maintained over an eight-month period of observation.

## RESULTS

Fourteen illustrative cases, which have been observed closely on the four-meal regimen, form the basis of this preliminary report. Ten of these had been under observation for *control periods* of one to six years prior to the institution of the new dietary arrangement, and hence afford a suitable basis of comparison. Our youngest patient was 18 years of age; the rest were from 40 to 72. Ten were women, four men. One was obese; two were well below the average weight for their height and age. Twelve of the patients were engaged in active occupations, including those of student, steel-mill laborer, and housewife. These patients were all maintained on relatively high carbohydrate diets (average over 180 gm.) both before and after the four-meal arrangement. All cases received, during their entire periods of observation, protamine zinc insulin in doses ranging from 10 to 100 units daily; several had received supplementary doses of soluble insulin in the earlier phases of their treatment. Criteria of improvement were based upon an evaluation of the individual patient's course, as previously noted, compared to that after use of the four-meal regimen, both periods being adequately checked by frequent blood sugar studies, urine test and weight records.

Our experience with these cases was uniformly favorable, and indicated that the four-meal regimen offered a means of circumventing the most objectionable features connected with the use of protamine zinc insulin. We feel that this regimen now enables us to realize in practice the simplicity of management originally expected from the use of the new insulin. Because we were able successfully to control even the most severe diabetics in this group with only one injection of protamine zinc insulin daily, we have not used supplementary doses of soluble insulin since. The results to date confirm our original experience with this preliminary group. The five patients in this series who had required one or more daily doses of soluble insulin previously, required none after the institution of the new feeding schedule (cases 1, 3, 6, 8, and 11); nor did they require food between meals to balance the action of such supplementary injections. Protamine zinc insulin was used more efficiently with four meals than with three, hence in six cases (2, 3, 4, 5, 6, and 8) a reduction in the daily amount of protamine insulin required was made possible. In our present practice we feel that the four-meal regimen allows the most convenient type of diabetic therapy since the advent of protamine zinc insulin.

Because of previous difficulties in attaining good diabetic control with the new product, some workers had concluded that the use of protamine zinc insulin was not compatible with the maintenance of physiologic levels of the blood sugar. Boyd,<sup>11</sup> for example, has reported that, in diabetic chil-



5. Overdosage of insulin provokes a reactive output of adrenalin from the suprarenal medulla (Brandt and Katz,<sup>22</sup> La Barre and Houssa,<sup>23</sup> Kugelmann,<sup>24</sup> etc.) and is sometimes followed by symptoms of angina pectoris (Hadorn,<sup>25</sup> Schönbrunner,<sup>26</sup> etc.);

6. An increased amount of adrenalin has been found in the blood during attacks of acute arterial hypertension which were accompanied by angina pectoris (Brandt and Katz<sup>22</sup>);

7. Attacks of angina pectoris in patients with tumors of the suprarenal medullar tissue are apt to subside completely after removal of the tumor (Lenhartz,<sup>27</sup> etc.);

8. There is a close similarity of the electrocardiogram after injection of adrenalin (Lepeschkin,<sup>28</sup> Vesa,<sup>62</sup> etc.) and during attacks of angina pectoris (depression of S-T, inversion of T, etc.); both of them being of the anoxia type (Büchner<sup>47</sup>).

9. The iodine level of the blood is increased after injection of adrenalin (Schittenhelm and Eisler,<sup>29</sup> Gutzeit and Parade,<sup>30</sup> etc.), after effort (Gutzeit and Parade,<sup>30</sup> MacCullagh and Roy,<sup>31</sup> Raab and Schönbrunner<sup>32</sup>), on psychic emotion (Schittenhelm and Eisler<sup>29</sup>) and during attacks of angina pectoris (Siedek<sup>33</sup>);

10. Angina pectoris is frequently improved through total thyroidectomy (Blumgart, Levine and Berlin,<sup>34</sup> etc.) which diminishes both the secretion of adrenalin and the response of the sympathetic system to adrenalin (Asher and Nakayama,<sup>35</sup> Oswald,<sup>36</sup> Reiss,<sup>37</sup> Bansi,<sup>38</sup> etc.); accordingly the painful reaction to adrenalin in patients with coronary sclerosis disappears after thyroidectomy (Eppinger and Levine<sup>39</sup>);

11. Roentgen irradiation of the suprarenal glands is followed by a reduction of their ability to produce adrenalin (Eisler and Hirsch,<sup>40</sup> David and Hirsch<sup>41</sup>) and even leads to destructive histological changes of the suprarenals if applied in a large dosage (Cottenot,<sup>42</sup> Tsuzuki,<sup>43</sup> Martin, Rogers and Fischer,<sup>45</sup> Engelstad and Torgersen<sup>46</sup>). Roentgen irradiation has furthermore proved to be a very potent therapeutic means in the treatment of angina pectoris (Raab,<sup>44</sup> Hadorn<sup>25</sup>). It also leads frequently to a partial or complete normalization of the pathological electrocardiogram of patients who have been subjectively improved or entirely freed of their complaints (Raab and Schönbrunner<sup>48</sup>);

12. The rise of blood iodine after effort which is probably due to an adrenalin effect was found diminished or absent in cases of angina pectoris after irradiation of the suprarenal glands (Raab and Schönbrunner<sup>32</sup>).

Against the assumption of an impaired dilatability of the coronary arteries, the objection could be raised, that the pain-relieving effect of nitroglycerin and other nitrites is due, according to general belief, to a dilatation of the coronary arteries. It is, however, not known whether the nitrites exert only a vaso-dilatory effect or whether they do not also diminish the sensitivity of the thoracic sympathetic nerves or the myocardial oxygen con-

10, 12). No reactions occurred in our series of cases throughout the entire period of observation during the new regimen. The protective value of the "fourth meal," as compared with the evening snack of carbohydrate as more generally employed, appears to be established.

We anticipated some difficulty with the new regimen since it involved a radical change in the patients' fixed habit patterns of three meals. We found, however, that diabetic patients as a rule, actually prefer a bite—usually more than a bite—in the evenings. The subjective response of the patients was gratifying. They felt satiated at meal times. They were more content and, therefore, more coöperative, on four feedings. Most of the patients had previously received multiple injections of insulin daily. Now they welcomed the simplified procedure of using one injection daily, and were encouraged by their improved blood sugar and urine reports. Almost every patient in the series maintained his weight or gained while on the four-meal regimen; none lost. No one has objected that the evening feeding was burdensome or impractical; on the other hand, none voiced preference for food between meals as previously given. The four-meal arrangement has proved particularly popular with our clinic patients. We rather believe, from the general improvement of that group, that dietary infractions were negligible in comparison with previous experience.

The gains achieved by the new four-meal regimen are reflected in the changed attitude with which we ourselves now approach the control of a new diabetic with protamine zinc insulin. The new regimen engenders a feeling of confidence regarding "difficult" cases. Patients with severe diabetes, who previously would have been recalcitrant to management with protamine zinc insulin, no longer appear as formidable problems, since we now have some assurance that we can safely, and in short order, raise the protamine insulin dosage until glycosuria is controlled, *without the usual danger of insulin reactions*. We know that any tendency toward nocturnal hypoglycemia will be prevented by the absorption of one-fifth or two-fifths of the daily carbohydrate allowance (even more if the occasion should warrant) from an evening feeding. Case 8 is particularly illustrative of a severe diabetic patient who was brought under excellent control with the four-meal regimen in about half the time that we had formerly required with similar cases. Such saving of time constitutes a great economic advantage to patient and hospital alike.

Patients with mild diabetes offer no great problem under the four-meal regimen. Our experience suggests that it is possible to use protamine zinc insulin in the treatment of mild diabetes safely and successfully in the office or clinic, with little or no necessity for hospital admission.

#### COMMENT

In the clinical use of protamine insulin we were confronted with a new situation in the treatment of diabetes mellitus. With its use we were forced

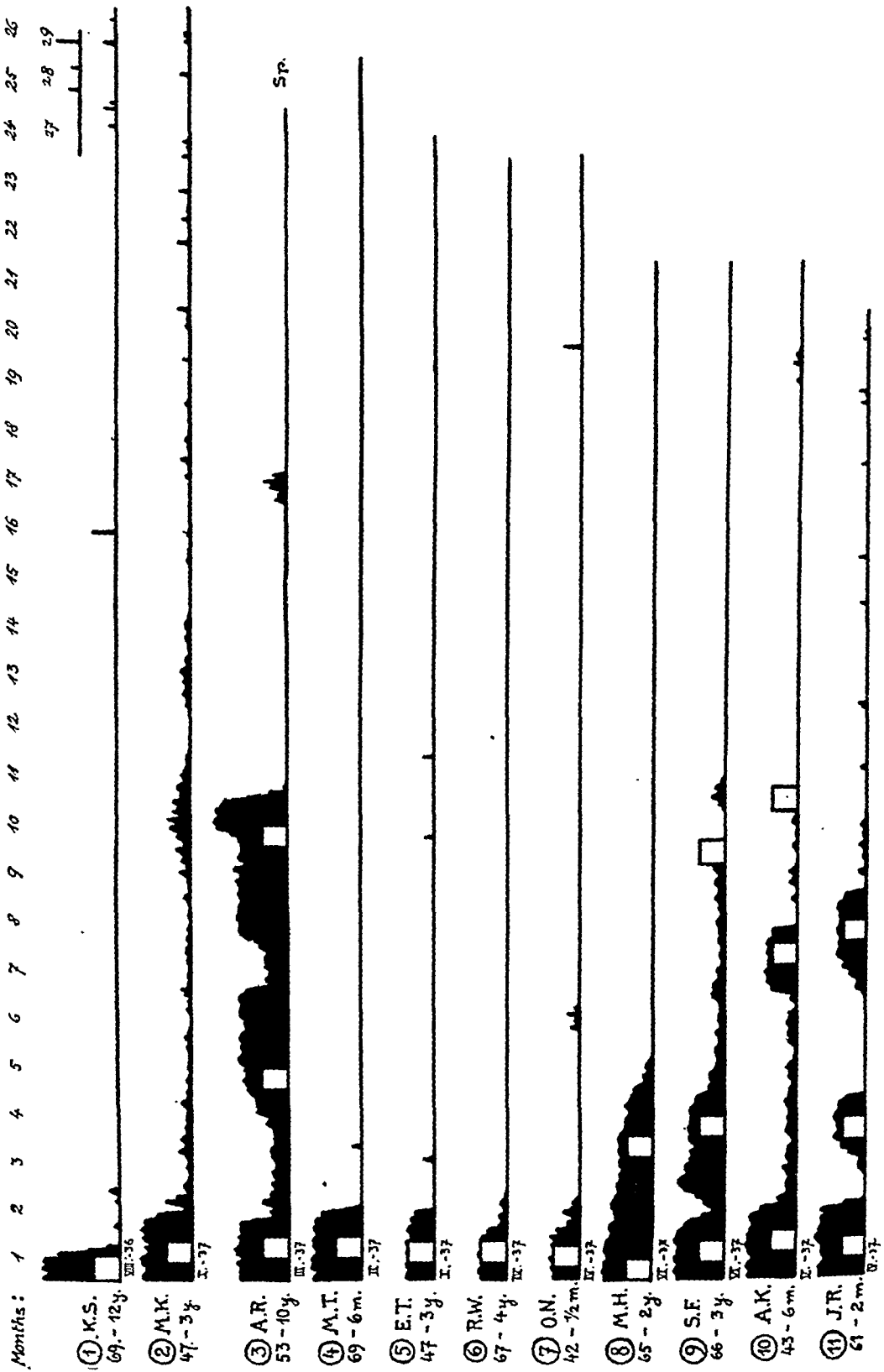


FIG. 2.

control. Neither supplementary doses of soluble insulin nor feedings between meals are necessary with this regimen.

2. Smoother, quicker, more adequate control of diabetes is made possible, even in severe cases, with minimal doses of protamine zinc insulin.

3. The grave danger of hypoglycemic shock, and hence the possibility of insulin fatalities, are eliminated by the use of a "protective fourth meal."

4. The satiety, contentment, and morale of diabetic patients are enhanced by the use of four meals daily.

5. The four-meal regimen makes the treatment of diabetes mellitus with protamine zinc insulin a safe and practical procedure for office and clinic use.

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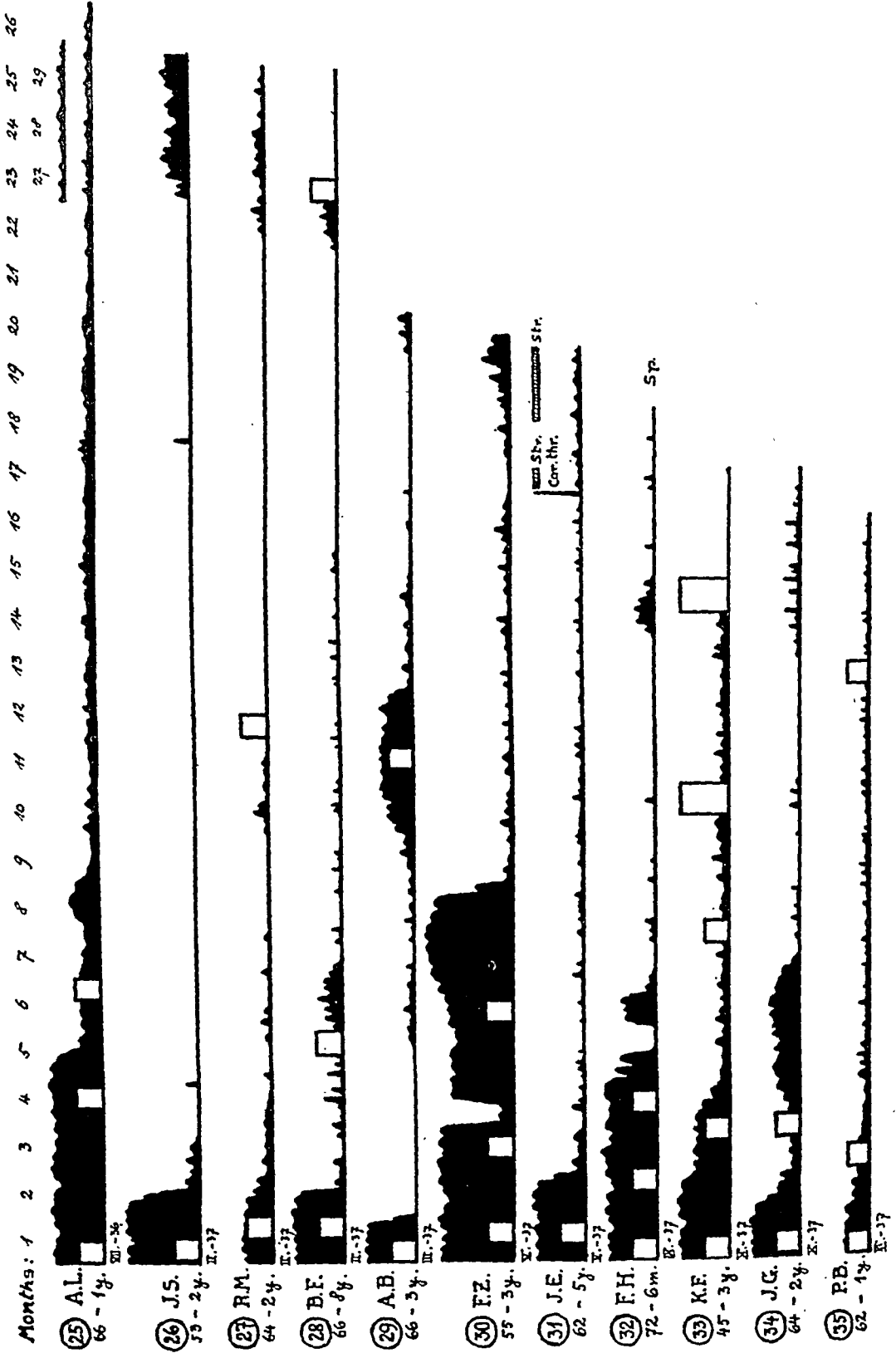
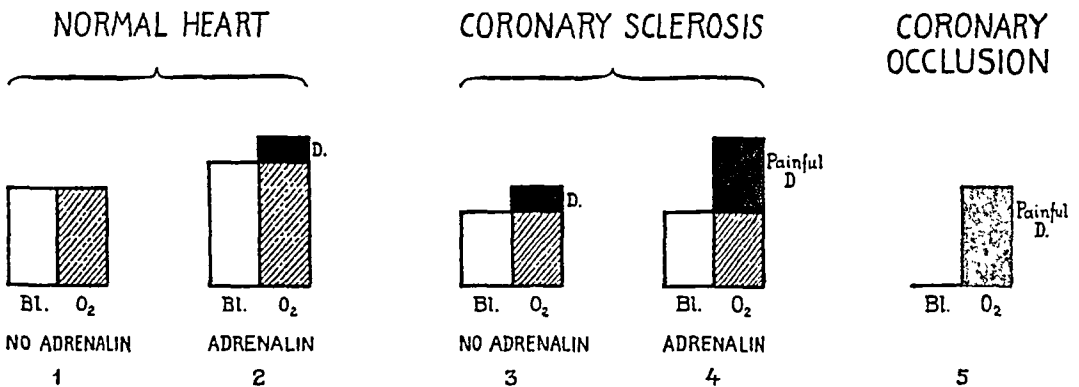


FIG. 4.

tion of these facts a theory is advanced that *angina pectoris on effort, on cold, on emotion, etc., is due to an acute anoxia of the heart muscle which is caused by the specific effect of sudden discharges of adrenalin from the suprarenal glands: increase of myocardial oxygen consumption, without adequate dilatation of the sclerotic coronary arteries* (figure 1).

As additional arguments in favor of this theory the following facts can be stated:

1. Subcutaneous injection of adrenalin produces anginal pain fairly regularly in patients with coronary disease but fails to do so in normals (Levine, Ernstene and Jacobson<sup>13</sup>);



Bl. = CORONARY BLOOD SUPPLY  
O<sub>2</sub> = MYOCARDIAL OXYGEN CONSUMPTION  
D. = MYOCARDIAL OXYGEN DEFICIENCY

- 1 O<sub>2</sub>-CONSUMPTION NORMAL.- BLOOD SUPPLY ADEQUATE
- 2 O<sub>2</sub>-CONSUMPTION INCREASED.- BLOOD SUPPLY ALSO INCREASED, BUT NOT SUFFICIENTLY TO PREVENT A SLIGHT PAINLESS OXYGEN DEFICIENCY
- 3 BLOOD SUPPLY IMPAIRED.- OXYGEN CONSUMPTION NORMAL. THEREFORE A SLIGHT PAINLESS OXYGEN DEFICIENCY
- 4 O<sub>2</sub>-CONSUMPTION INCREASED BUT BLOOD SUPPLY SUBNORMAL. THEREFORE A STRONG OXYGEN-DEFICIENCY AND ANGINAL PAIN.
- 5 BLOOD SUPPLY LACKING - O<sub>2</sub>-CONSUMPTION NORMAL. THEREFORE A STRONG OXYGEN DEFICIENCY AND ANGINAL PAIN.

FIG. 1.

2. In an experiment which I carried out on myself, then at the age of 32, a subcutaneous injection of a large dose of adrenalin (1.3 mg.) resulted in an attack of distressing anginal pain with a typical anoxic electrocardiogram;

3. Inhalation of low oxygen concentrations leads both to discharge of adrenalin (Cannon<sup>1</sup> and others) and in patients with coronary disease to anginal pain (Rothschild and Kissin<sup>14</sup>);

4. Nicotin causes discharges of adrenalin (Cannon, Aub and Binger,<sup>15</sup> Eichholtz,<sup>16</sup> Stewart and Rogoff,<sup>17</sup> Strauss,<sup>18</sup> Short and Johnson<sup>19</sup>) and frequently produces attacks of angina pectoris in patients with coronary sclerosis (Külbs,<sup>20</sup> Denecke,<sup>21</sup> Strauss,<sup>18</sup> etc.);

there had occurred attacks of coronary thrombosis according to the history but no patient was submitted to roentgen irradiation of the suprarenals unless a space of at least several months had elapsed after the last attack. Seventy-five patients were smokers although of different degrees; many of them had ceased smoking soon after the onset of their disease. Fifty-three suffered from stenocardiac pain, not only on effort, etc., but also at rest and at night. Eighty-five per cent of all patients were males.

The duration of the complaints before beginning of roentgen treatment had varied widely between two weeks and 23 years. A great majority of the patients had undergone other treatment before irradiation, mostly without effect or with unsatisfactory result: nitrites, iodine, Padutin, papaverin, combinations of theobromin and barbituric acid, etc. Twenty-eight patients had received euphyllin or analogous preparations and six had been given strophanthin injections. Seventy-three had used nitroglycerin which gave temporary relief in 69 and was ineffective in four of them.

#### EFFECT OF IRRADIATIONS UPON ANGINAL SYMPTOMS

The graphic tracings of the intensity and frequency of stenocardiac complaints before and after roentgen treatment show a complete or almost complete disappearance of the symptoms of angina pectoris for at least three months and up to 28 months in about 40 per cent of the cases. A considerable improvement from at least 6 up to 24 months was noted in about 20 per cent. A moderate improvement from 6 to 17 months was reported in about 15 per cent and no improvement at all in about 25 per cent. The average duration of improvement in the first two groups (+++ and ++ ) together was  $13\frac{1}{2}$  months and in the third group (+)  $7\frac{1}{2}$  months.

Irradiation of the chest was added to that of the suprarenals in 18 cases in which the latter alone seemed to be insufficient or not at all effective. In six of them it apparently caused a further improvement, probably due to a diminution of intrathoracic nervous sensitivity as it has been assumed by Gilbert<sup>53</sup> and others.

The patient's own judgment is in most of the cases the only standard to be used in evaluating the therapeutic effect of any treatment in angina pectoris. For this reason I sent inquiries to those patients who could still be located during the first months after my departure from Europe (December 1938) in order to complete their history. Among 60 answers which I received there were 48 statements of a persisting satisfactory condition or of further improvement. Two patients reported recent relapses. Two of my oldest patients who had been bed-ridden for years before the roentgen treatment, because of daily frequent severe attacks (numbers 1 and 43) were almost completely free from pain for a total period of 28 and 20 months respectively. They could walk and climb stairs without discomfort. Patient 3, a merchant, who according to his own statement "had not been able to do the easiest kind of work before the treatment" has now applied for

sumption or both. Kretz<sup>49</sup> and others have expressed doubts concerning a purely vaso-dilatory mechanism of the effect of nitrites in angina pectoris. Riseman and Brown<sup>50</sup> have observed an analgesic effect of nitroglycerin also in pain of non-cardiac origin.

No definite explanation can be given at present for the not infrequent absence of anginal complaints in patients with severe coronary sclerosis. It seems, however, that besides suprarenal activity a second extra-cardiac factor is essential for the occurrence of stenocardiac pain, namely, an abnormal sensitivity of the thoracic sympathetic nerves (Morawitz,<sup>51</sup> Edens,<sup>59</sup> etc.).

### ROENTGEN IRRADIATION OF THE SUPRARENAL GLANDS

The therapeutic effect of roentgen irradiation of the suprarenal glands has been studied over a period of two and a half years on one hundred patients with angina pectoris. None of them showed signs of marked cardiac decompensation. The technic of treatment consisted in series of six single treatments on consecutive days; three times on the left side and three times on the right side; each treatment 200 to 250 r, 0.5 mm. Cu plus 1 mm. Al, 180 KV, 4 MA; size of fields 10 by 15 centimeters.

With only very few exceptions all patients were treated outside of the hospital under their habitual living conditions. Most of them were kept under regular control at intervals of two months on an average. In every case an approximate graphic record of the intensity and frequency of anginal complaints was made (figures 2 to 8), the height of the black areas indicating their severity. Every small white square represents one series of irradiations of the suprarenals; the larger ones represent series of irradiations of the chest according to the suggestion of Lian,<sup>52</sup> Gilbert,<sup>53</sup> Sussman,<sup>54</sup> Wasch and Schenck,<sup>55</sup> etc.

As a rule no other treatment was allowed besides the roentgen irradiations except nitroglycerin and some rather ineffective theobromine-luminal combinations (Purartial, etc.) provided that they had been used before. Only in a few instances which are recorded on the charts, euphyllin preparations or strophanthin or iodine were given for a limited time.

The diagnoses were based on the history and on the description which the patients gave of their typical complaints. Electrocardiograms at rest and after exercise (running up stairs) were recorded in 38 of the cases. Twenty-three of them presented pathological alterations either of an anoxia type (19 cases) or indicating a disturbance of intraventricular conduction. In 20 patients whose complaints suggested the presence of some continuous neuralgic factor besides the typical stenocardiac complaints during exercise, emotion, cold, etc., spinal arthritic changes were detected through roentgen examination of the thoracic spinal column (indicated as "sp." on figures 2 to 8). Four patients (15, 25, 51, 55) had syphilis, one of them (51) with aortic insufficiency. In seven cases (7, 17, 21, 39, 41, 69, 78)





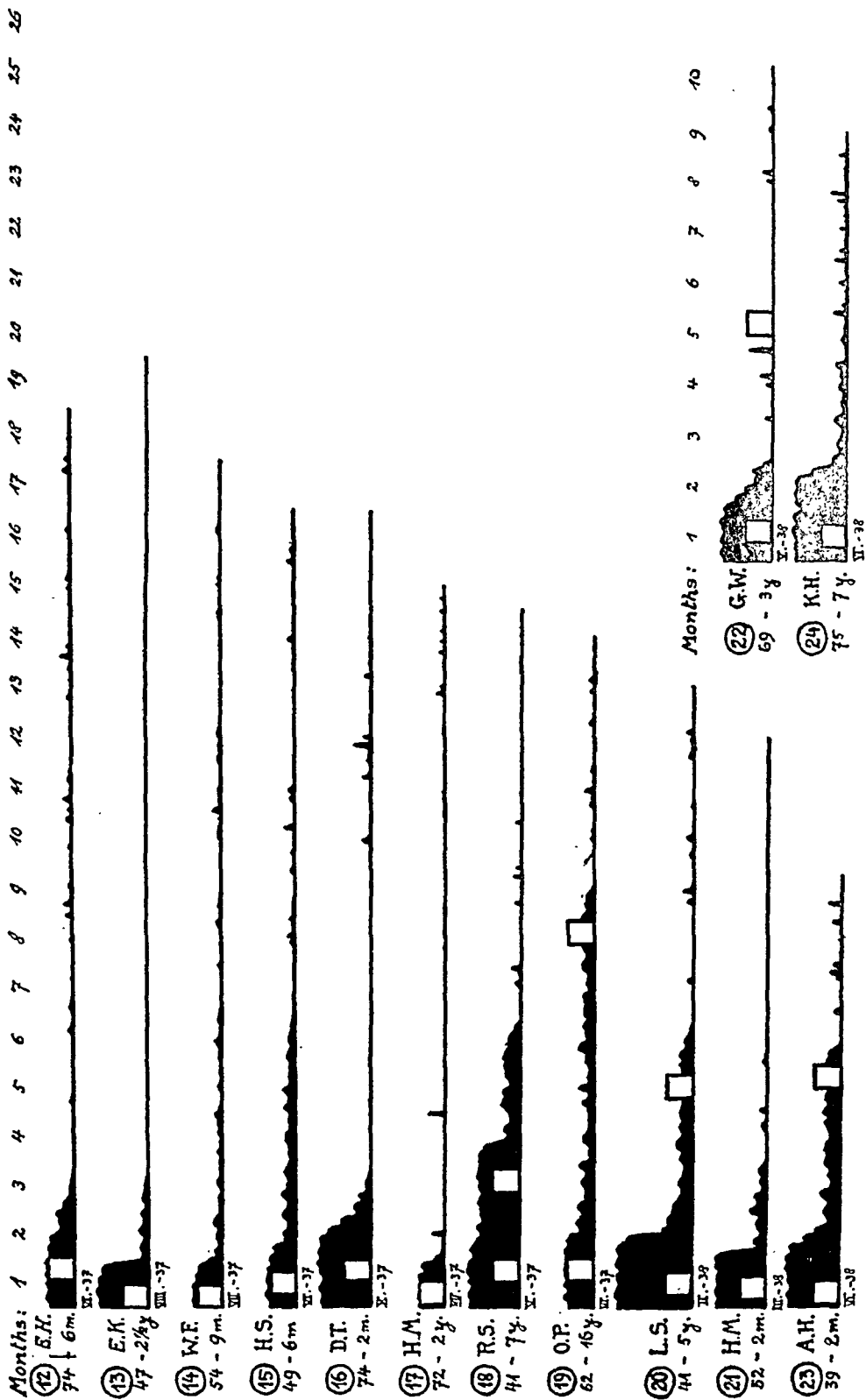


FIG. 3.

admission as a field laborer in a country into which he wants to immigrate. Patient 8 writes that in spite of the "terrible excitement" which she had to go through before leaving her native land, there was no relapse and that "a short time after the treatment the pressure near the heart as well as the pain in the left arm seemed to be blown away." An opera singer (number 13) writes "I have sung 85 great operas in this season without the slightest effort while before the irradiations I had very often more or less severe pain in the heart region." Four patients (2, 3, 34, 36) had resumed their habitual sport of mountain climbing, one of them (number 36) up to a height of 7000 feet. In this latter case the difficulty in walking had been so great before the treatment that the patient's daily walk from his home to his office, which was two-thirds of a mile, used to take him about 45 minutes. Patient 18 who was 41 years of age was able to take up strenuous physical training in a voluntary military formation after his long lasting anginal symptoms had disappeared. In 42 of the letters the writers ascribe the improvement of their condition expressly to the roentgen treatment. Many of them emphasize the complete or almost complete disappearance of their complaints, they report that they are again able to walk fast and to climb stairs, that they are no longer bothered by cold weather and that they have been able to reduce or to entirely omit the use of nitroglycerin.

A confirmation of the therapeutic efficiency of roentgen irradiation of the suprarenals in angina pectoris has been reported by Hadorn (Berne). In a recent personal letter he refers to a "sometimes amazing" improvement of the clinical state in about two-thirds of 25 irradiated patients and to several instances of normalization of the electrocardiogram after irradiation. Redisch (New York) has followed 11 cases of angina pectoris over one-half to one year after irradiation of the suprarenals. Seven of them (about two-thirds) were greatly improved insofar as the attacks disappeared almost entirely, two were moderately improved and two did not respond to the treatment. One of the latter died. Among the improved patients three series had been given in three cases, two series in three cases and one series in one case. Five of them were hypertensives. The blood pressure was not noticeably lowered.

Further personal communications in regard to good results from roentgen irradiations of the suprarenals in angina pectoris have been obtained from Prof. Schittenhelm (head of the Medical Clinic of the University of Munich) \* who reported several cases of striking improvement without a relapse, lasting for two years, and from several practicing physicians of Vienna. Hutton<sup>55</sup> (Chicago) mentions the disappearance of precordial distress in five cases of arterial hypertension after combined irradiation of the pituitary and the suprarenal glands. Only von Zimmermann-Meinzinger<sup>56</sup> (Vienna) claims in a short note that the roentgen irradiation of the suprarenals is ineffective except for a "transitory psychogenic effect" and rejects it for undisclosed reasons.

\* Received in September 1940.

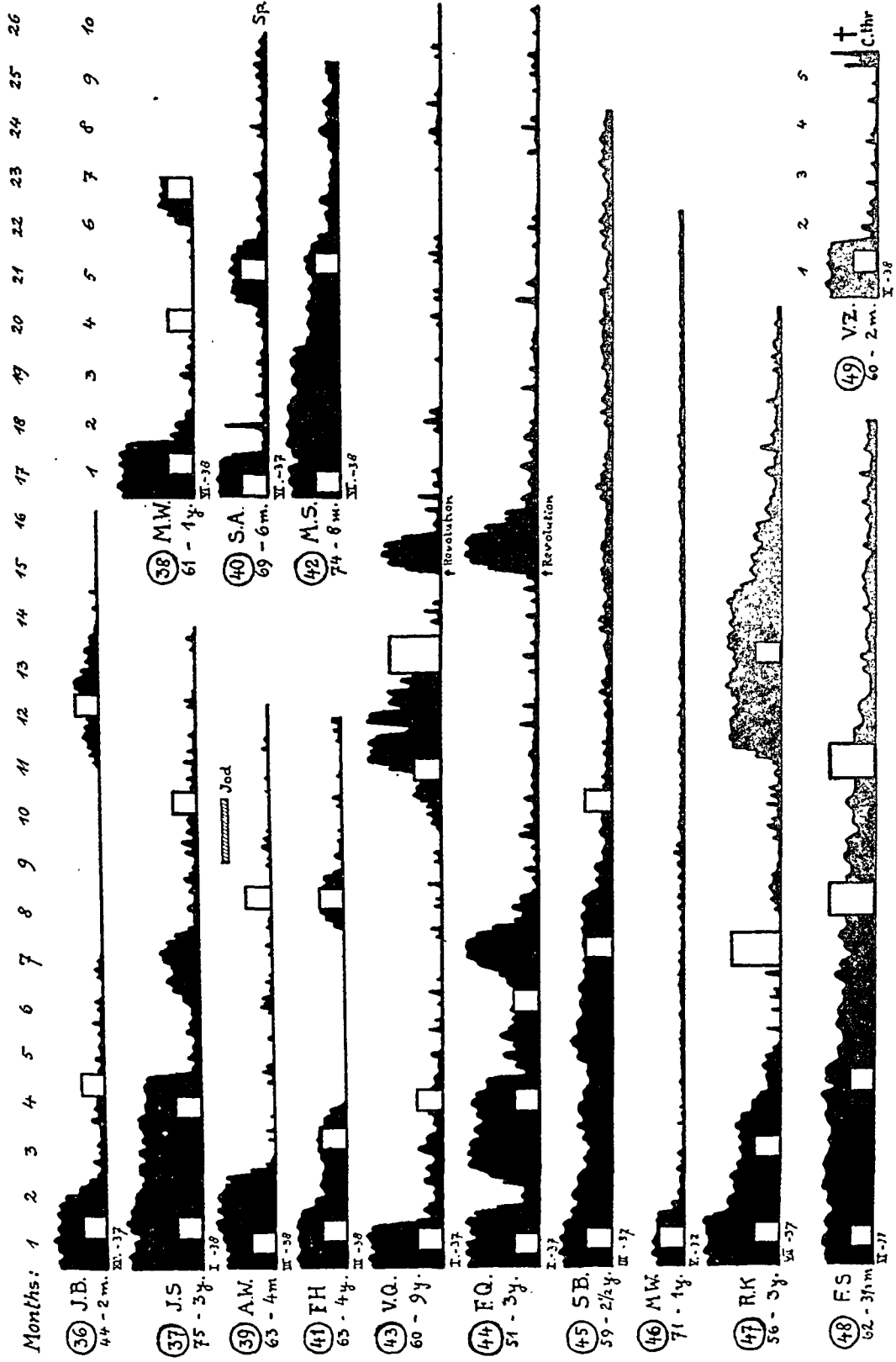


FIG. 5.

of course, that the number of failures in the latter group could have been reduced by a further extension of the treatment. This is made obvious by the example of other cases in which the first series seemed almost or wholly ineffective while a second or third series was successful (for instance, cases 3, 8, 18, 25, 30, 32, 33, 37, 44).

Intervals of two to four months between single series seemed to be appropriate to provide for an optimal increase in efficiency.

#### ONSET OF IMPROVEMENT AFTER IRRADIATION OF THE SUPRARENALS

The onset of improvement took place at intervals varying from a few days to two months after the decisive series of irradiations; in most in-

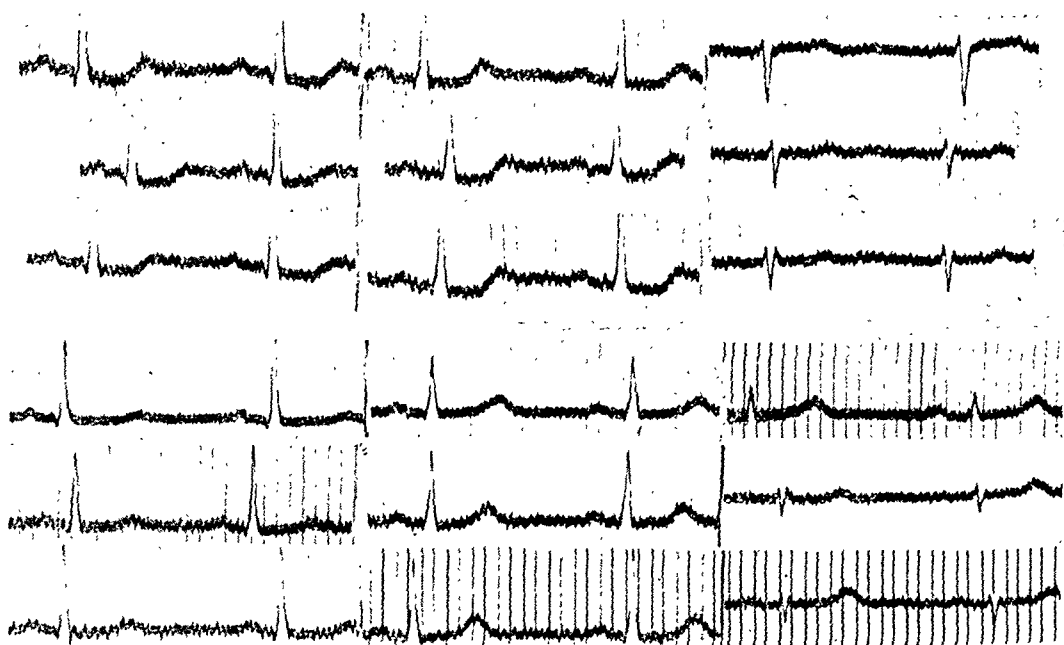


FIG. 10. Case 8, M. H., 65 years, ♀.

Above: Electrocardiogram at rest and after exercise before first treatment.

Below: Six months after second series of irradiation (for four months completely free of complaints).

stances, however, it was observed between the second and fourth week. This corresponds with the experimental findings in animals, whose suprarenal glands showed beginning histological changes in from a few days up to six weeks after irradiation (Cottenot<sup>42</sup>).

#### RELAPSES

Relapses of various degree and duration occurred in 20 among 76 improved patients. Some of them were only slight and disappeared soon by themselves (numbers 3, 32, 37, 43, 44), other ones could be stopped or at

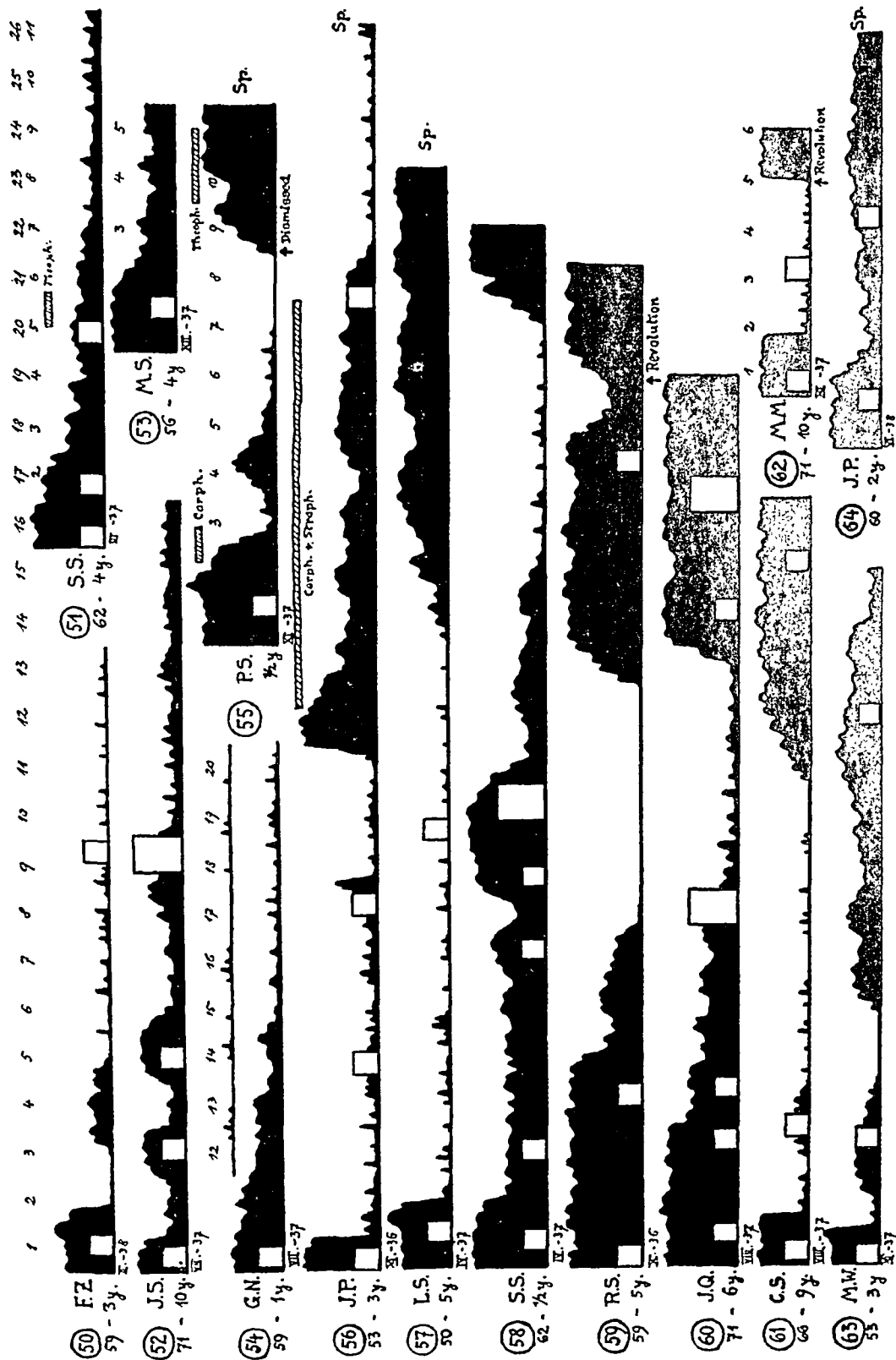


FIG. 6.

ing the irradiations. It usually did not last but a few days, to be succeeded by partial or complete disappearance of the complaints. This phenomenon reminds one of the transitory reactions of the irradiated thyroid and of experimental findings concerning a transient hyperfunction of the suprarenal glands after irradiation. It has been observed chiefly in those few cases where attempts were made to give a larger dosage (300r per session). Following these experiences the large doses were abandoned.

Nausea occurred in about 15 per cent of the cases during and immediately after the roentgen series but was distressing in only two or three instances in a total number of 224 series of treatments. More than 80 per cent of the patients did not complain of any discomfort whatsoever in connection with the treatment.

### BEHAVIOR OF BLOOD PRESSURE

The arterial blood pressure was 160 mm. Hg or more before treatment in 41 per cent of the cases. In none of them was a definite effect of the

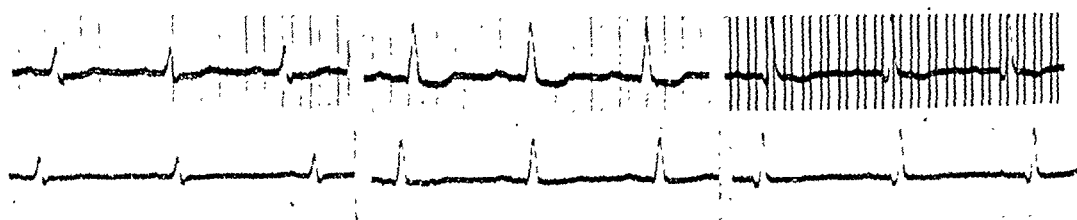


FIG. 12. Case 50, F. Z., 59 years, ♂.

Above: Electrocardiogram at rest before first treatment.

Below: Eight months after first series of irradiation (after seven months of considerable improvement, temporarily free of complaints).

irradiations upon the blood pressure observed. Some of the extremely hypertensive patients were more or less completely freed of their stenocardiac complaints without any lowering of the systolic pressure (for instance numbers 2, 8, 16, 32, 37, 49). In fact the blood pressure was often somewhat increased after the treatment (table 1). This is further confirmation of

TABLE I

Degree of Improvement after Irradiat.	Number of Cases	Degree of Complaints			Average Duration of Complaints (years)	Average Number of Series of Irradiations	Average Duration of Improvement (months)	Number of Relapses		Systolic Blood pr. (mm. Hg)		Average age (years)	Number of Deaths
		Severe	Medium	Slight				Total	Improved by Irradiations	Before Treatment	After Treatment		
+++ and ++	62	24%	58%	18%	3½	2	13½	20	12	155	158	60	1
+	14	43%	57%	0%	1¾	3	7½	9	3	151	161	61	0
-	24	50%	33%	17%	5½	2	—	—	—	172	180	60	2

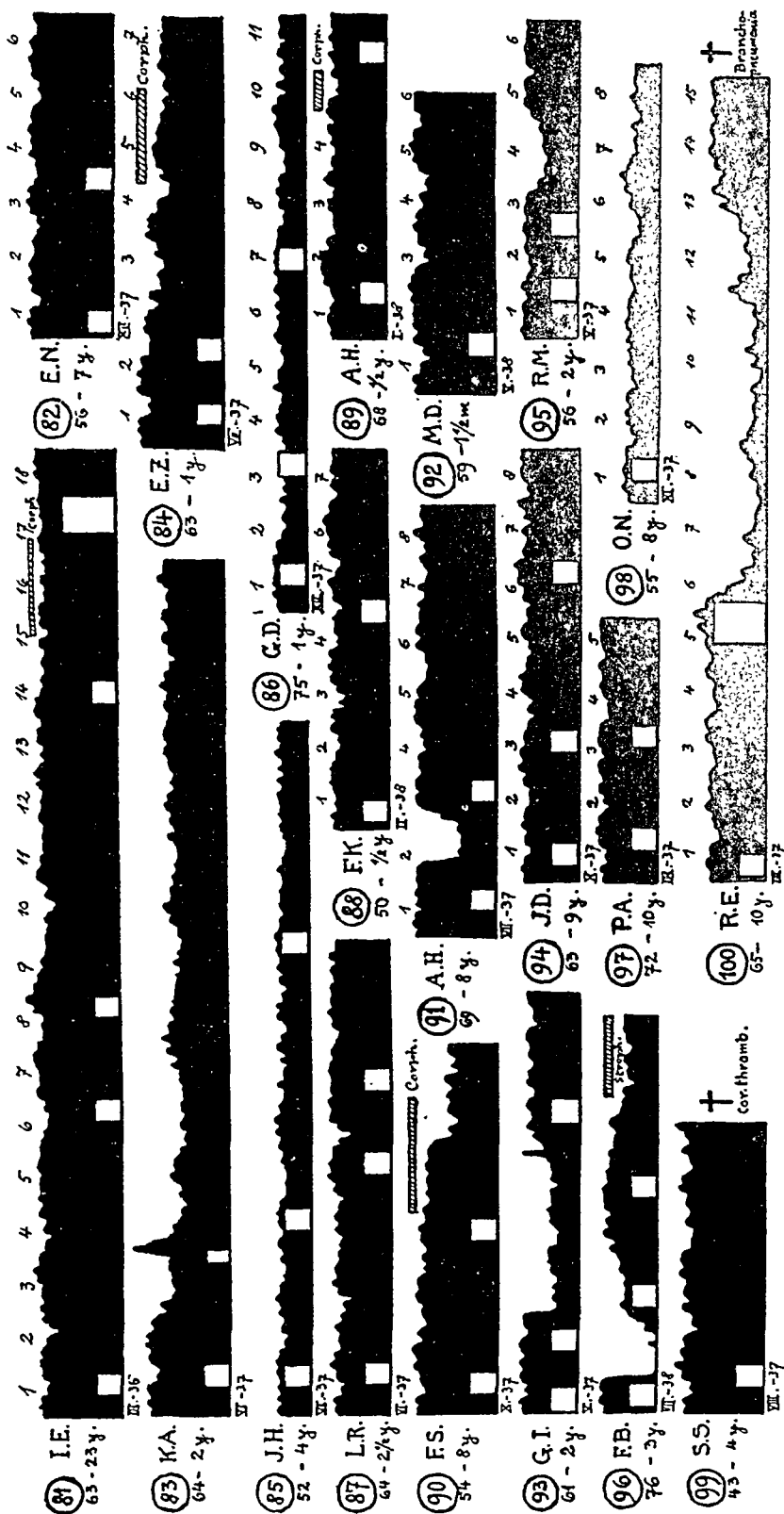


FIG. 8.



developed coronary occlusion, both within three days *before* the date fixed for the first irradiation. It is not possible, therefore, to draw any conclusion in either sense concerning an influence by irradiation of the suprarenals upon the tendency toward coronary thrombosis and death.

### CONTRAINDICATIONS

Contraindications for irradiation of the suprarenals have to be deducted from theoretical assumptions rather than from actual unfavorable experiences. The following may be mentioned: (1) Any symptoms of primary insufficiency of the suprarenal glands, (2) A coronary thrombosis within the past three months, (3) Tuberculosis of the kidneys or of the peritoneum, (4) Cardiac decompensation (insofar as no long-lasting improvement was seen in five severely decompensated patients with attacks of pulmonary

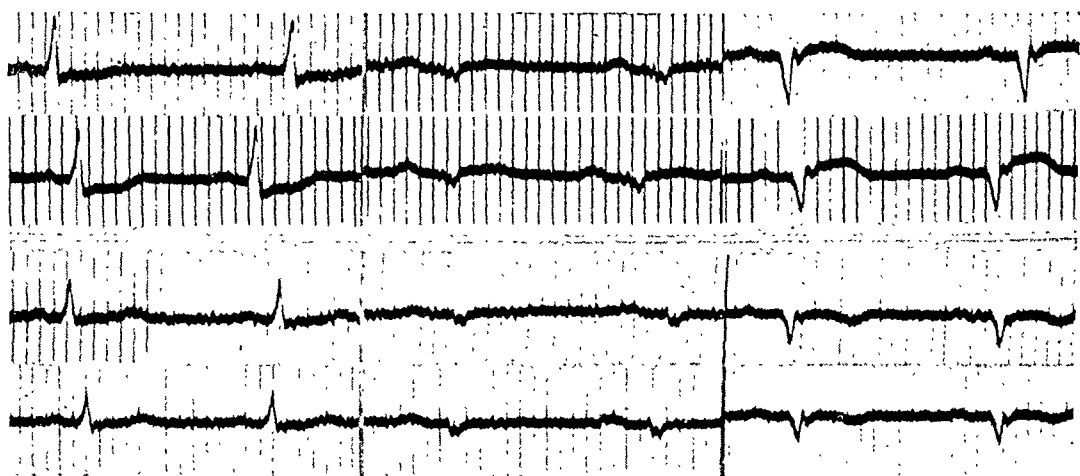


FIG. 14. Case 41, F. H., 63 years, ♂.

Above: Electrocardiogram at rest and after exercise before first treatment.

Below: One and a half months after the first series of irradiation (after five weeks of improvement).

Four months after the second series of irradiation, during which time the complaints had disappeared completely, the electrocardiogram was found unchanged.

edema, in spite of a few weeks' relief from pain in three of them). These cases are not included in the statistics of this paper.

### REASONS FOR FAILURE OF ROENTGEN TREATMENT

A definite explanation for the complete failure of roentgen therapy in about one-quarter of all cases cannot be given. As table 1 shows, there were no differences in the average age of these patients and those in the other groups. The average blood pressure was only slightly higher in the non-reacting group. The average duration of the disease was longer than in the well responding patients and also the degree of the complaints was somewhat higher in the majority of non-responding patients. These two

A certain participation of psychogenic factors in the improvement of some of the cases is possible, of course, but it is certainly not decisive. This becomes evident from the fact that the subjective improvement does not take place earlier than several days or weeks after the irradiations, as a rule. Two or three series are not infrequently needed to produce a noticeable effect and in many patients other "impressive" treatments (injections, operations etc.) had been tried before without success. Finally the often very long-lasting absence of complaints after the irradiations, even in very severe cases, speaks clearly enough against a merely psychogenic effect.

#### NORMALIZATION OF THE ELECTROCARDIOGRAM

In 38 cases the electrocardiogram was examined before and after treatment. In 10 out of 13 improved patients who had shown signs of myocardial anoxia (depression of S-T flattening or inversion of T-wave) the electrocardiogram was found partly or completely normalized after roentgen-irradiation of the suprarenals (figures 9 to 14). This never oc-

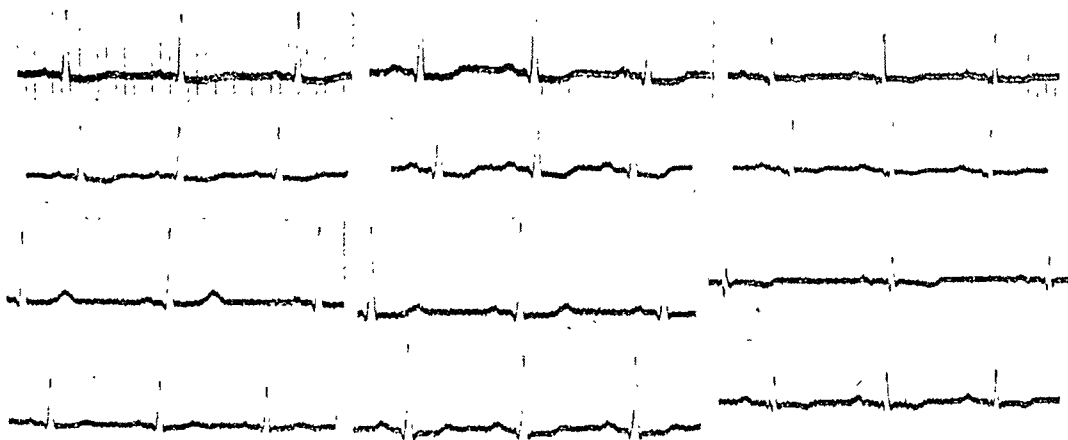


FIG. 9. Case 22, G. W., 69 years, ♂.

Above: Electrocardiogram at rest and after exercise before first treatment.

Below: Two months after first series of irradiation (for one month free of complaints).

curring in patients whose complaints were not improved. Analogous findings were recorded by Hadorn,<sup>25</sup> according to a personal communication. Further comments on these observations have been published in *Archiv für Kreislaufforschung* by Raab and Schönbrunner.<sup>48</sup>

#### NUMBER OF SERIES OF IRRADIATIONS

In 21 cases one single series proved to be more or less sufficiently effective. Among the other 55 patients who were improved to various degrees, two series had been given in 22 cases, three series in 26 cases, and four series in 7 cases. The entirely unsuccessful treatments in 24 cases amounted to from one to four series with an average of two. It is possible,

duration of  $13\frac{1}{2}$  months. Fourteen patients were moderately improved during an average of  $7\frac{1}{2}$  months and 24 did not respond at all.\*

Electrocardiographic signs of myocardial anoxia disappeared partly or completely in most of the successfully treated patients, but remained unchanged in those whose complaints were not improved.

The blood pressure, either high or normal, remained practically unchanged in all instances.

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\* Since the conclusion of the above paper new reports were received from four of the patients described. Number 51 reported that he had spent 24 months without anginal attacks, numbers 12 and 14 were free of complaints for 21 and 13 months respectively after which time a slight relapse seemed to have begun in number 14. Number 22 was "quite satisfied" with his condition during 8 months (an additional series had been given in June 1939).

In recent time 12 patients have been treated in Burlington by Dr. A. B. Soule. Two of them have not yet responded, 10 were completely or partly freed of their attacks for an average duration of 5 months up to date; nine of these 10 patients had received only one series.

least improved through renewed irradiations (numbers 10, 11, 28, 29, 30, 36, 40, 41, 43, 47, 52, 63, 66, 67, 74). In a few instances the relapse was not essentially influenced by further treatment of the suprarenals (numbers 60, 61, 69) or the treatment was discontinued (numbers 26, 55, 57, 58, 62, 68, 77).

Special attention has been paid to the effect of excitement and fear upon those 23 patients who belonged to the Jewish race and who had been improved through roentgen treatment. Only six of them (numbers 43, 44, 59, 62, 67, 77) suffered from a sudden relapse of their complaints immediately following the introduction of antisemitic laws into Austria after the reunion of that country with the German Reich (March 1938). In November 1938 when severe reprisals were taken for the assassination of a German diplomat by a Jewish youth, 16 of the aforementioned 23 Jewish patients were still under observation. None of them developed a relapse at

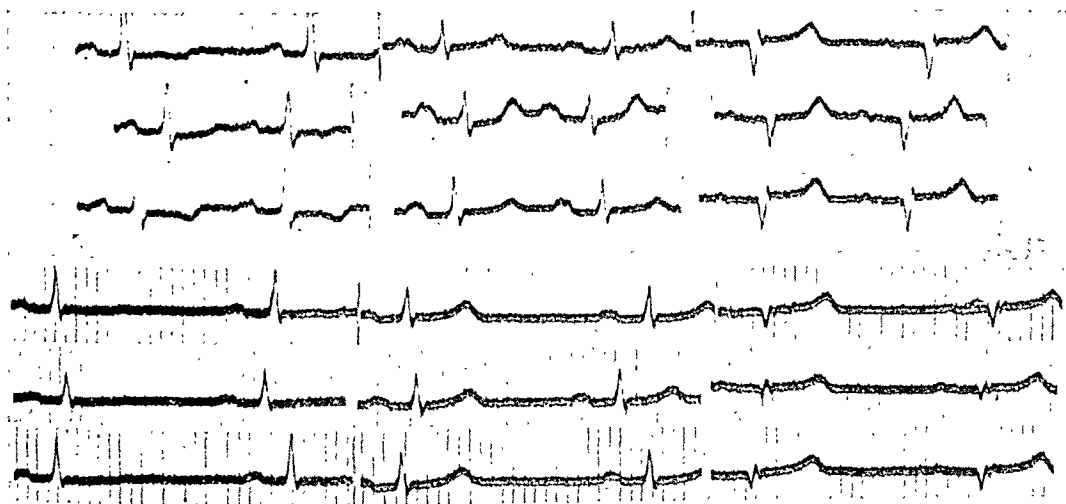


FIG. 11. Case 10, A. K., 43 years, ♂.

Above: Electrocardiogram at rest and after exercise before first treatment.

Below: Two and a half months after second series of irradiations (for two months almost free of complaints).

Seven and a half months after third series, during which time the complaints had disappeared completely, the electrocardiogram was found unchanged.

this time. In one case (number 55) a relapse occurred after the patient had lost his job.

#### BY-SYMPTOMS OF THE IRRADIATIONS

In no instance were there any signs of a *pathological* reduction of suprarenal activity such as general weakness, arterial hypotension, general hyperpigmentation, etc. No alterations of the irradiated skin occurred except for a slight brownish local discoloration in some instances. In several cases (numbers 3, 30, 43, 44, 50, 55, 56, 58, 63, 83) there was a slight or marked increase of stenocardiac complaints during or immediately follow-

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the fact pointed out in another publication (Raab<sup>57</sup>) that the symptoms of angina pectoris are not essentially dependent upon the degree of mechanical strain put on the heart muscle through peripheral hemodynamic resistance. The average height of blood pressure before treatment in the group which did not respond to the irradiations was slightly higher than that in the groups which showed improvement (172 mm. Hg vs. 155 and 151 mm. Hg). Redisch's cases also did not show any change of blood pressure after irradiation whereas a lowering of blood pressure in essential hypertension can be produced through combined irradiation of the suprarenals and the pituitary gland according to Hutton.<sup>55</sup>

#### OCCURRENCE OF CORONARY THROMBOSIS AND DEATH

Seven patients had had thrombosis of the coronary arteries, according to their history, some time before the beginning of the irradiations. Six of these patients responded well to the treatment. The electrocardiogram which was taken in two of them after treatment was found partly normalized.



FIG. 13. Case 17, H. M., 72 years, ♂.

Above: Electrocardiogram at rest before first treatment.

Below: Three months after first series of irradiation (for two months free of complaints).

In three cases (numbers 31, 49, 99) a coronary thrombosis occurred several months after the irradiations, in two of them with fatal result.

Death occurred in the aforementioned case number 99 (4½ months after the first series) from coronary occlusion and in case number 100 from bronchopneumonia (14 months after the first series). In both of them the irradiation of the suprarenals had been ineffective. Patient number 49 seemed to be greatly improved at first—although his electrocardiogram remained unchanged—but he died from an attack of coronary occlusion four months after the irradiations. Besides these three deaths there were three other fatalities not included in the statistics of this paper because they occurred too early (one week, 8 days and 18 days) after the first series of irradiations. All of these patients died apparently from coronary occlusion. In one of them a fresh thrombus was found at necropsy. Whether or not these latter events had any causal connection with the foregoing irradiations cannot be decided. It should be emphasized, however, that sudden death is a common feature in angina pectoris and that one patient died and another

research in all branches of medicine. As consultants and teachers they have broadened the outlook of medical students, interns, and the profession at large. By their efforts, methods and implements of precision making for speedier and more accurate diagnosis have been developed and extended freely to the larger group of practitioners. They have stimulated the exhibition of specific treatment in various conditions, particularly those of an allergic nature, physiologic disorders, bacterial and virus infections, and functional disabilities of previously obscure etiology. Failing this group of so-called sub-specialists, we should indeed be years behind our present stage of accomplishment, and far below our present level of quality.

It may be of interest and should be of value to us all to consider the present status of sub-specialization in relation to a number of groups, including that of the specialists themselves, the rest of the profession (particularly internists), and the community at large. A number of questions at once present themselves. For example: How many sub-specialists should there be in proportion to all practicing internists, and what should be their relation to the rank and file of physicians? How should they be trained and developed? What should be their relation to the public?

The answer to the question of size must depend upon the nature of the sub-specialists' activity. That is to say, are they to serve merely as consultants and teachers, or should they make themselves directly available to the public? If they are to serve the profession primarily, then obviously there should be only a relatively few seasoned, high-grade consultants, whose primary function is to instruct and consult with physicians, to teach medical students and interns, and to further investigative work in their individual fields. If, on the other hand, the sub-specialists permit themselves to accept and treat patients directly, they must swell their number.

The problem of number brings up the next question, that of the training and development of young men in the special fields. How wise is it for a man after completing internship or residency to leap at once into allergy, gastroenterology, cardiology, and so forth, to the exclusion of general medical practice? Certainly if the apparent demand on the part of the public for such services increases, it will become almost obligatory for him to do so. Perhaps some of you believe that the best type of consultant in the sub-specialties has emerged from the ranks of internal medicine after some years of exposure to various types of cases, *in addition* to emphasis on one particular group. No doubt some of you think otherwise. In any case, we can give our attention to the whole subject without prejudice, and perhaps with some benefit to internal medicine in the future. Certainly no one can answer these questions categorically; but before an audience like this, composed largely of men representing internal medicine as practicing internists, among whom presumably there are less than 16 per cent representing the sub-specialties solely, the problem at least merits discussion, and it would seem relatively safe for me to express a few personal opinions on the subject.

Not long ago in a large teaching hospital a colleague of mine—a well-

latter points may be of a certain importance but, nevertheless, there were also cases of the severest kind and of long duration among those who were almost entirely relieved of their complaints after the treatment (for instance numbers 1, 3, 20, 28, 31, 43).

The fact that stimulation of the sympathetic fibers of the heart produces the same reactions as adrenalin (specific increase of oxygen consumption with dilatation of the coronary arteries; Gollwitzer-Meier and Krüger<sup>58</sup>) suggests the possibility of a primary hyperirritability of the thoracic sympathetic nerves in certain cases which cannot be directly influenced by irradiation of the suprarenals but obtain benefit by irradiations of the chest (numbers 33, 48, 58, 100). Also the formation of adrenalin by the sympathetic neurones within the heart muscle itself (Cannon and Lissák<sup>60</sup>) may be of importance in these cases.

#### INDIVIDUAL EVALUATION OF THERAPEUTIC EFFICACY

As one or even two series of irradiations prove insufficient in some cases to give considerable and lasting relief, a patient must not be considered as definitely resistant to this therapy before three series have been applied at intervals of six to eight weeks and before a total observation period of five to six months has elapsed.

Furthermore attempts with other treatments must be avoided during this time, except for the use of nitroglycerin, if it is intended to draw clear conclusions.

#### SUMMARY AND CONCLUSIONS

1. *Theory*: Attacks of stenocardiac pain on effort, psychic emotion, cold, etc., are caused by anoxia of the heart muscle. This is largely due to acute discharges of adrenalin from the suprarenal glands occurring physiologically under the conditions mentioned.\* Adrenalin exerts a specific anoxiating effect upon the heart muscle which is under normal circumstances compensated by simultaneous dilatation of the coronary arteries. This compensatory mechanism must fail when the coronary arteries are unable to dilate adequately due to coronary sclerosis and thus an abnormally exaggerated painful degree of myocardial asphyxia will result.

2. *Therapy*: Attempts to relieve the symptoms of angina pectoris by restricting the acute discharges of adrenalin through roentgen irradiation of the suprarenal glands were successful in 76 out of 100 patients. These patients had typical attacks of angina pectoris on effort, etc.; several cases were of the severest kind. Sixty-two patients were entirely or almost entirely freed from complaints or, at least, considerably improved for an average

\*During the past year (1939-40) the correctness of this theory could be further evidenced through chemical determination of suprarenal hormonal compounds in the blood of normal individuals and of patients with angina pectoris at rest and after physical exercise, before and after roentgen treatment of the adrenal glands, and in the heart muscle of rats under similar experimental conditions. The results of these investigations are to be published at a later date.



an expert in a sub-specialty, how can we expect the man on the street to do other than to reflect their attitude by going directly to the office of a psychiatrist, a gastroenterologist, an expert in hypertension, in asthma, or even in dreams?

In this connection let us recall what was said by C. M. Jones,<sup>1</sup> past president of the American Gastroenterological Association, in his presidential address in 1937. After tracing the development of knowledge about the gastrointestinal tract, and mentioning certain men responsible for such progress (Beaumont, Pavlov, Roentgen, Cannon, Castle, Dale, Gamble, Ewald, Cushing and Banting among others), he continued:

“In spite of the many obvious omissions and deficiencies in the above list of men, it is clear that progress in gastroenterology, whether that term be taken to mean the science, the clinical understanding, or the therapeutics of digestive diseases, has never emanated from a group of men whose sole interest was necessarily directed toward a study of the gastrointestinal tract. Practically none of the men whose names are mentioned above could by the broadest stretch of imagination be classed as gastroenterologists. In other words, it is most essential that the members of a gastroenterological association be interested in and capable of discussing a multiplicity of apparently unrelated medical subjects, and that a practicing gastroenterologist must be equally catholic in his information, interests and training, if he is to give adequate and intelligent service to his patients. I am becoming more and more convinced that the scope of an association such as this must be kept a wide one, and that emphasis must be constantly placed, not on the narrow concept implied in the term gastroenterology, but upon a much broader and better balanced conception of the subject and its practice. *The only real danger lies in attempting to narrow the field*, and to my mind any attempt to emphasize the specialty rather than the special interest spells a lowering of values and a diminution in the quality of medical service.”

For me to suggest how specialists in medicine should be trained would indeed be presumptuous, even if it were entirely pertinent to the question at hand, but let me quote a few sentences spoken by Dean Burwell<sup>2</sup> of the Harvard Medical School at your last year's meeting in New Orleans, when discussing postgraduate medical education.

“Not only may special groups become concerned with parts of people and lose touch with the wider problem of the whole patient,” he said, “but such groups may actually become isolated and lose some essential contact with other fields. This may not be very serious for the first generation of specialists in a given field, but it might be really grave for their students or their students' students. This suggests to me the daring hypothesis that perhaps no group should be wholly responsible for the training of its own successors. Is it not one of the advantages of bi-sexual reproduction that sons do not in all respects resemble their fathers?”

Now if, as I fondly hope, some of you agree with me that a tendency

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of hypertension, of asthma, of tachycardia, of nocturia, of heartburn, or even insomnia? God save the mark!

Fortunately, internal medicine is still in a reasonably healthful condition, and no doubt will remain so. Moreover, we can all give it a hopeful prognosis, knowing as we do how deeply planted are its roots. The parent body is growing steadily in numbers and in strength. It will undoubtedly survive this minor malady. The very fact that we are aware of a trend which threatens to overreach itself demonstrates that the cure or correction is already half accomplished.

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## SPECIALIZATION IN INTERNAL MEDICINE\*

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EXAMINATION of the roster of our College reveals that most of us are practitioners of internal medicine, indicating that we are primarily interested in the diagnosis and treatment of all medical diseases. Merely by being Fellows in this College, we not only avow such interest, but assert our ability to solve diagnostic problems and to undertake the treatment of patients. Of course, as the pathologist so often attests, all of us are diagnostically vulnerable, and therefore cannot claim infallibility; but in the main, most of you will, I think, agree with this description of our membership.

Let us break down the figures that appear in the 1939 Directory, so that we may learn just how you have designated yourselves in the realm of internal medicine. Among approximately 3000 Fellows, 899 of you state simply that you are practitioners or teachers of internal medicine; 1183 of you apparently practice internal medicine, and in addition a medical specialty, such as cardiology, allergy, gastroenterology, psychiatry and the like; 323 of you are not in active clinical practice, being radiologists, pathologists, officers in the Public Health Service, the Army or the Navy; 100 of you have retired; and approximately 484 of you (or 16 per cent) state that you practice a medical specialty solely. It is quite possible that this last figure is not entirely accurate, and might prove to be lower if we could get a personal report from each man who placed himself in a sub-specialty without including the whole field. However, those are the figures, and they must be accepted. And in a way, they are rather comforting. By that I mean that it is reassuring to find that only 16 per cent of our Fellows find themselves exclusively in the narrower fields of medical practice. Without considerable study it would be impossible to determine just how many of these 484 men have withdrawn from the large field in order to concentrate, and how many have started from scratch, so to speak, as medical specialists. It is to be hoped, at any rate, that the larger proportion of them fall into the first category, namely that of well-trained and experienced internists who have found their forte as consultants and teachers in the sub-specialties.

At this point a word about the place of sub-specialization in medicine would seem to be in order. None of us can doubt the high value of such endeavor among medical men. The extraordinary advance in our profession during the last 25 years has rested in no small measure upon the accomplishments of well-trained internists in the special fields of cardiology, gastroenterology, endocrinology, allergy, hematology, neurology, the control of infectious disease, and others. These men have refined diagnostic procedures, established standards of treatment, and given impetus to scientific

\* Read at the Cleveland meeting of the American College of Physicians, April 1, 1940.

time that he was able to find only 20 authenticated cases. He reported ducts in the mass of pancreatic tissue, but was not certain that they opened into the lumen of the bowel. The mass was found in the jejunum. It was his impression that accessory pancreatic tissue located in such places might cause diverticuli, intussusception, or obstruction of the intestine.

One year later, in 1904, Turner<sup>7</sup> reported another case of aberrant pancreas, located in the jejunum, in a 15 year old female. He stated that the accessory pancreas in this instance contained ducts that opened into the bowel. He stated that such rests were not common and were significant because they might sometimes be the starting point of tumors in unusual locations. Also, in 1904, Warthin<sup>8</sup> reported two cases. In one, the pancreatic tissue was located in the greater omentum, and in the other, it was found in the anterior wall of the stomach.

Lewis,<sup>9</sup> in 1905, reported a case discovered at autopsy in which the aberrant tissue was located 85 cm. below the pyloric orifice, and noted that the ducts were apparently patulous. He stated that the condition was frequently found in lower animals, and not infrequently in man. He also advanced the idea that such aberrant masses of pancreatic tissue might prevent diabetes mellitus, as the accessory organ might escape the disease affecting the main organ in this disease.

Finkelstone,<sup>10</sup> in 1911, stated that this condition was not rare, and in the same year reported an aberrant pancreas in the wall of the intestine located 30 cm. from the pylorus. Gibson,<sup>11</sup> in 1912, reported an aberrant pancreas in the pyloric end of the stomach. The patient's gastrointestinal symptoms were so persistent and severe that the abdomen was explored. The mass of pancreatic tissue was removed from the wall of the stomach; however, the same symptoms returned later, and it was evident that the accessory pancreas had not caused them.

In 1913, Weidman<sup>12</sup> reported an aberrant pancreas located in the capsule of the spleen. Also, in 1913, Carwardine<sup>13</sup> reported an accessory pancreas in a girl 12 years of age. It was located in the jejunum. The symptoms were those of obstruction of the bowel. Exploration revealed the nodule to be in a state of acute necrosis with swelling of the bowel in this region, causing almost complete obstruction. Posterior gastrojejunostomy was performed, but the patient died. Autopsy was refused. He stated that an accessory pancreas might give trouble by one or more of four methods; viz., "(1) it may produce mechanical alterations in the walls of the alimentary canal; (2) the accessory pancreas is liable to acute pancreatitis; (3) accessory pancreas may complicate the diagnosis of the cause of abdominal complications; (4) accessory pancreas may develop chronic interstitial pancreatitis."

In 1916, Weidman<sup>14</sup> reported another case in which the pancreatic tissue was located in the duodenal wall. In this same year, Weidman<sup>15</sup> again reported a case, this time located in the wall of the jejunum.

An aberrant pancreas located in the duodenum was reported by Reimann<sup>16</sup> in 1918. The patient was 54 years old, a male who had diabetes mellitus and a duodenal ulcer. During this same year Benjamin<sup>17</sup> reported an accessory pancreas that caused intussusception in the upper part of the jejunum. The pathological diagnosis of the case was adenoma of aberrant pancreas.

In 1921, Cafritz<sup>18</sup> reported an interesting case in which because of epigastric pain, vomiting, and a long tender appendix retaining barium at 72 hours, he

trained internist—was asked by a fourth-year student: "In your own private practice do you treat cases of coronary thrombosis?" More recently a young medical intern inquired of another medical friend: "Do you treat lobar pneumonia in your private practice?" Now, both of these questions were put in good faith by serious-minded young men just entering the profession, and reflected, it seems to me, an attitude to be deplored. The mystery shrouding cardiology and the study of diseases of the chest seemed to them at the moment impenetrable. Such an attitude makes one wonder just what is the trend in the education of internists. The trouble apparently starts early in a young man's medical training today, certainly during the fourth year, perhaps even earlier. He sees a patient admitted to the ward for diagnostic study and assigned to him. Not infrequently before he has had time to obtain an adequate history, examine the patient, or give his difficulty thoughtful consideration, occasionally even before the case has been properly reviewed by the men in charge, there appear on the record one or more expert opinions by various consultants. Often under such conditions the diagnosis is quickly made and treatment is advised. What results? The student is apt to accept the verdict as final, say to himself "Well, that's that," and pass on to other duties. The only person who has advanced himself intellectually is the consultant. The younger man does not know quite how the thing has been done, but is willing to believe in the result, still retaining his mystification as regards the expert. In such an atmosphere, one can well understand how the men quoted above came to put their questions to my confrères.

Please do not misunderstand me. Such a situation is by no means the rule in our teaching centers; but this hypothetical episode does serve to illustrate a distinct tendency in contemporary medical education, a tendency that some of us believe must be combated.

Our young graduate, after finishing his internship and perhaps his residency, now has to consider his future. Shall he face the troublesome complexities of general internal medicine, or shall he attempt to tear away that cloud of mystery surrounding some specialty and become at once an expert himself? There is nothing, of course, to prevent his learning a medical specialty while he continues his work in medicine, but often the narrower path appears much smoother, and, incidentally, the financial returns quicker and larger. The latter aspect, that of earning a comfortable livelihood, is again modified at once by the number of men joining him in sub-specialization. If the public demand for his specialty becomes quickly filled—following the law of supply and demand—he must then resort to the practice of general internal medicine, certain features of which he may have neglected; and because of such neglect there is always the possibility that he will practice it to the detriment of the public.

We know that the competent, seasoned specialist-consultant prefers *not* to be consulted directly by patients; but if young students and interns (who are to become practitioners) have acquired the habit of turning at once to

located in a dermoid cyst in the anterior mediastinum of the chest. Preoperative diagnosis was intrathoracic goiter. Removal was successful.

King and McCallum<sup>31</sup> reported four cases in 1934, and offered evidence that aberrant pancreatic tissue was not a "cell rest" and did not arise during embryonic life. They believed it arose from differentiated tissue usually developing in adult life. The reasons given for believing this were that such tissue was directly or indirectly connected with the overlying epithelium, and that in some cases direct continuity could be established between the pancreatic tissue and gastric epithelium. In addition, distribution of such tissue in the stomach corresponded to the usual locations of gastric ulcers. Furthermore, the tissue was usually found in adults and old people. Another reason was that there was no morphologic connection between these masses and the anatomic pancreas; and the final ground for the belief was that the aberrant masses were not discrete, but were intermingled in localized areas with normal structures of the wall of the stomach.

Best and Bowers,<sup>32</sup> in 1934, stated that the condition is a defect of embryological development and is a surgical condition not often producing symptoms. They further pointed out that when symptoms are produced they are usually interpreted as being due to cholecystitis, peptic ulcer, or malignancy.

In 1935, Hunt and Bonesteel<sup>33</sup> reported a case in which the aberrant tissue was located in Meckel's diverticulum and in which the symptoms resembled those of appendicitis. These authors reported the fourteenth case recorded in this location. They presented a summary of cases with location, up to 1932, as shown in table 1.

TABLE I  
Distribution of Aberrant Pancreatic Tissue as Found by Hunt and Bonesteel

Location	Warthin 1904	Horgan 1921	Simpson 1927	Hunt and Bonesteel 1932	Total	%
Wall of stomach	14	8	25	12	59	31.7
Wall of duodenum	10	4	14	12	40	21.5
Wall of jejunum	13	13	10	3	39	20.9
Wall of ileum	1	1	2	0	4	2.1
Wall of intestine (not located)	1	1	1	0	3	1.6
Diverticulum of stomach	1	0	2	0	3	1.6
Diverticulum of duodenum	0	2	0	1	3	1.6
Diverticulum of ileum	2	3	4	4	13	7.0
Meckel's diverticulum	3	1	6	3	13	7.0
Umbilical fistula	1	0	0	0	1	0.5
Mesenteric fat	1	0	0	0	1	0.5
Omentum	1	0	0	0	1	0.5
Splenic capsule	0	1	2	0	3	1.6
Gall-bladder	0	0	1	1	2	1.1
Total cases	49	34	67	36	186	

In 1935, Branch and Gross<sup>34</sup> reported 24 cases collected from the records of the Boston Children's Hospital and the Peter Bent Brigham Hospital. Four of these cases produced pathological changes; viz., one causing pyloric obstruction, and the other three, ulceration of the stomach or duodenum.

Also in 1935, Poppi<sup>35</sup> reported a series of 300 cases, which is the most complete to date. These were collected from the literature since 1727. In some

toward too early and too frequent specialization exists in the ranks of internal medicine, and that such a tendency deserves some restraint—if you believe, in other words, that we should make an attempt to put our house in order in that regard, then what are you willing and able to do about it? There is much that *can* be done.

First of all, those of you who are teachers in medical schools and hospitals can accomplish much through your personal influence upon students, even during their earlier years. Let them understand the value of independent approach to all medical problems; inspire in them the ambition to “see through” for themselves, and to voice their opinions before calling upon the experts. Teach them the value of consultation and how to make intelligent use of consultants. Convince them that the exercise of their own intellectual equipment is of far greater importance than being right—that being wrong is not of itself a cardinal sin. Show them that the man who is always “right,” the man who knows all the answers, is more often wrong than right. As the students grow older, advancing to the practice of their profession, urge upon them some special interest, demanding that they keep themselves the while exposed to all types of cases, both in the clinic and, as may happen, in private practice. Demonstrate to them the fallacy of attaching themselves exclusively to any instrument of precision, pointing out to them the spectacle of the well-known tail wagging the dog!

Further, what can you specialists do for these young men? Among other things, you can put freely at their disposal all the details of your specialty, encourage their interest in your special field, inspire them to take up investigative studies, show them the interrelation between your limited field and the other branches of medicine—and, in the process of so doing, learn much from them yourselves. Yours is a high responsibility, because without you the quality of medical practice would suffer much. But if you go hand in hand with the great body of internists, directing your efforts properly, the future progress of internal medicine remains secure.

Lastly, what can all of us as internists-at-large, that is to say, as physicians, do to attain the desired objective? To begin with, we can back up whole-heartedly the bona fide, well-trained and seasoned specialists. We can see to it that their path is made easy for self-training and for the teaching of selected younger men. We can use them as consultants to the advantage of ourselves, our patients, and incidentally to themselves. We can discourage their segregation, particularly by welcoming them into our larger groups and societies, and by opposing the formation of numerous minor groups. Above all, we must prevent as far as possible the establishment of minor qualifying boards. In any event, the National Board of Internal Medicine should be the fundamental qualifying body, the starting point, at least, from which men may, if it seems necessary, go on to further qualification by boards of narrower scope. But is it possible that the day will come when a man will be qualified to engage in the treatment



to those cases reported by Poppi, five cases in the ileum, five cases in Meckel's diverticulum, and two cases in the splenic capsule.

In reviewing the literature since 1932 a number of cases have been found which were not included by either Poppi<sup>25</sup> or by Hunt and Bonesteel<sup>23</sup> in their reports. These cases, with those found reported since 1935, are listed in table 3.

The distribution of aberrant pancreatic tissue in the gastrointestinal tract, as far as we have been able to determine from available reports, including the case reported in this paper, is given in table 4.

TABLE IV  
Distribution of Aberrant Pancreatic Tissue with Percentage Incidence

	No. of cases	%		No. of cases	%
Stomach	95	25.67	Diverticulum (not located)	1	.27
Duodenum	105	28.37	Umbilical fistula	1	.27
Duodeno-jejunal angle	2	.54	Mesentery	3	.81
Jejunum	65	17.56	Omentum	4	1.08
Ileum	18	4.85	Splenic capsule	3	.81
Small intestine (not located)	6	1.62	Spleen	1	.27
Diverticulum of stomach	3	.81	Gall-bladder	3	.81
Diverticulum of duodenum	7	1.89	Cystic duct	1	.27
Diverticulum of jejunum	1	.27	Gastro-colic ligament	1	.27
Diverticulum of ileum	8	2.16	Transverse mesocolon	1	.27
Meckel's diverticulum	21	5.67	Location questionable	18	4.86
Diverticulum of small intestine (not located)	2	.54	Total Cases	370	

#### CASE REPORT

J. H. B., a white male, aged 43 years, was admitted to Walter Reed General Hospital, Washington, D. C., on April 12, 1938. His previous personal and family history is not important. He entered the hospital complaining of diarrhea, generalized abdominal pain, anorexia, and weakness. These symptoms were not related in any way to meals. They had been present for more than a year, and the patient had been hospitalized five months previously, at which time a careful study of the gastrointestinal tract had been made with negative findings. The general physical examination revealed obesity (weight 208 pounds), slightly enlarged thyroid, moderate generalized abdominal tenderness on deep palpation, chronic follicular tonsillitis, and edentulous maxillae. Laboratory and roentgen-ray examination revealed a polyp located in the pyloric end of the stomach (figure 1), an absence of free hydrochloric acid in the gastric juice, with only slight response after the administration of histamine, and a repeatedly low basal metabolic rate (minus 25 per cent to minus 47 per cent).

Because of the belief that the polyp was the cause of the gastrointestinal symptoms, resection was recommended. A subtotal gastrectomy was done, and the following pathological report was received: "Grossly: a cup-shaped section of the wall of the pylorus of the stomach, approximately 5 cm. in diameter. The base of the depression presented a teat-like elevation upon the mucosal surface. Microscopic: Three sections were studied. The mucosa was of ectopic intestinal type; the glands (Lieberkuhn) were long, and lined with cylindrical mucous cells. Some of the glands were cystic and included mucus, and polymorphonuclear leukocytes. The lymphoid tissue was hyperplastic. The muscularis mucosa was intact. The submucosa included (a) many glands of Brunner type; (b) quite a large compact fragment of pancreatic

# CASE REPORTS

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## ABERRANT PANCREAS, WITH REVIEW OF THE LITERATURE AND REPORT OF A CASE \*

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KLOB first reported the aberrant pancreas in 1859. Since then pancreatic tissue has been frequently found in various organs of the abdominal cavity. Defective embryological development is probably responsible for small masses of pancreatic cells being pulled off from the main organ in the developmental process. These small masses may be found in almost any part of the gastrointestinal tract and are located usually between the mucous and serous layers. The histology of aberrant pancreatic tissue is not different from that of the main organ.

There is also evidence in the literature that these aberrant masses are at times the site of or the origin of carcinoma. At operation the tissue is frequently mistaken for some type of tumor. Some of the aberrant pancreatic masses seem to have normally formed ducts that open into the lumen of the bowel. In other instances, gastrointestinal disturbances are caused by the mechanical effects due to the growth of the aberrant tissue. It is interesting to note the impressions of some of those who have reported cases in the past.

Montgomery,<sup>1</sup> as early as 1861, reported two cases. One was his own case, in which the tissue was located in the jejunum. He was not able to find any ducts in this one. The other case was one that had been written up in the autopsy book nine years previously by Dr. Bristowe, who identified pancreatic tissue located in the ileum.

In 1888, Van Gieson<sup>2</sup> reported two cases with pancreatic tissue situated in the duodenum. One was found in a newborn child causing obstruction of the bowel, and the other was in an adult male. Note was made by him at the time of the danger of mistaking such masses for carcinoma.

Thatcher<sup>3</sup> reported an accessory pancreas in 1893, and Biggs,<sup>4</sup> in the same year, reported a supernumerary pancreas in the pylorus of an alcoholic. He stated at the time that this anomaly would be found in nearly one-third of all necropsies, if careful search were made. It was also his opinion that ducts were found throughout such tissue, but not well marked, and that he could not say where the ducts emptied.

In 1900, Nicholls<sup>5</sup> reported an aberrant pancreas in the duodenum discovered at autopsy in a young boy with tuberculosis of the lumbar vertebrae. Three years later, in 1903, Ruediger<sup>6</sup> reported an accessory pancreas and stated at the

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We wish to express our grateful appreciation to the Army Medical Museum, Washington, D. C. for the preparation of the photomicrographs.

ach, and jejunum, in order. Meckel's diverticulum and the ileum are also fairly frequent sites. Defective embryological development is the most likely explanation of the occurrence of this anomaly. In the stomach, as in the case presented, the tissue frequently appears as a polypoid mass on roentgen-ray examination, and at other times it may appear as an ulcer. It is impossible, obviously, to diagnose pancreatic tissue in any location, except by microscopic examination of

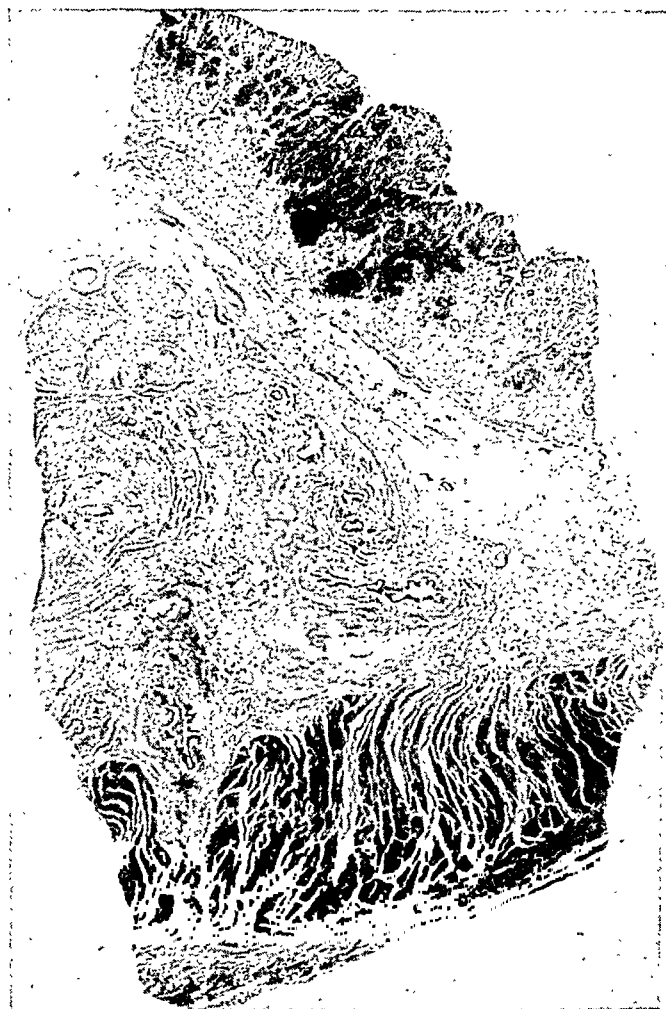


FIG. 2. Photomicrograph of mass removed from stomach showing a cross section of the wall of the stomach and collections of pancreatic tissue in the submucosa. (Army Medical Museum, No. 67778, Acc. No. 60222.)

tissue removed at operation or at autopsy. When the tissue is located in the stomach, as in the case reported, its removal does not always relieve symptoms. In the stomach, as elsewhere, it may be the site of acute inflammation, perhaps with ulceration or necrosis; and, when located in the ileum, it may occasionally cause intussusception. If these changes are present surgical removal is indicated, and, if successful, will undoubtedly relieve the acute symptoms.

explored the abdomen. No pathological process was found except a chronically inflamed appendix, and an aberrant pancreas located in the duodenum, which he removed. He concluded that the accessory pancreas did not cause symptoms in this case, but in similar cases should be removed provided the true pancreas was normal in appearance, size, and consistency.

In 1921, Horgan<sup>19</sup> reported two cases. One was located in the duodenum and the other in the posterior wall of the stomach, near the greater curvature. Also in 1921, Cohen<sup>20</sup> reported an aberrant pancreas located in the pylorus producing among other gastrointestinal symptoms that of partial obstruction. There was a gastric ulcer over the mass in the wall of the stomach. It was his belief that chemical irritation of adjacent tissues by pancreatic juice should be considered, and he thought this was the cause of the ulcer in his case. He also mentioned obstruction, ulcer, intussusception, diverticuli, and pancreatitis as the surgical complications that might be expected in aberrant pancreas.

Choisser,<sup>21</sup> in 1925, reported an aberrant pancreas located in the pylorus. The mass was discovered at operation and was thought to be a carcinoma. It was removed and later identified by pathological study as an accessory pancreas.

Weeks and Steinke,<sup>22</sup> in 1927, reported a case in an infant girl two months old. The accessory pancreas was located in the duodenum. Exploration and later autopsy studies revealed, in addition to the aberrant pancreas, congenital atresia of the bile ducts and biliary cirrhosis. Also in 1927, Simpson<sup>23</sup> reported a case in which the pancreatic tissue was located in the wall of the stomach and resembled a gastric ulcer.

Cave,<sup>24</sup> in 1928, reported a case in which the tissue was located in the duodenum. This case mimicked clinically a duodenal ulcer.

Moore<sup>25</sup> reported a case in 1929. The pancreatic mass was located in the jejunum in an infant one year old. The child died from laryngeal obstruction. He concluded with the opinion that the origin of these congenital anomalies was either by adhesions of the main anlage or from anomalous anlage, and that accessory pancreases were in rare instances the underlying cause of diverticuli and intussusception, and the site of the origin of carcinoma.

Also in 1929, Cox<sup>26</sup> reported an aberrant pancreas located in the pylorus near the pyloric ring, which apparently produced partial obstruction. Nausea, vomiting, epigastric pain, loss of appetite, sleeplessness, and loss of weight were the principal symptoms. He also reported a reduced amount of hydrochloric acid. Exploration revealed an aberrant pancreas located in the pylorus which was removed. A gastroenterostomy was performed, which apparently relieved the patient.

Farr,<sup>27</sup> in 1930, reported an aberrant pancreas located in the jejunum. There was also a duodenal ulcer with marked obstruction and gastric retention.

In 1931, Ross<sup>28</sup> reported a case very similar to one previously reported by Benjamin,<sup>17</sup> in which intestinal intussusception was caused by an aberrant pancreas. Ross described the mechanism of the production of the intussusception. The diagnosis was adenoma of aberrant pancreas, and Ross stated at the time that his was the second case recorded in medical literature of aberrant pancreas causing intussusception.

Bookman,<sup>29</sup> in 1932, reported an aberrant pancreas in the duodenum in which carcinoma developed. In the same year Crosby and Graham<sup>30</sup> reported a case

## CONCLUSIONS

1. The literature on aberrant pancreatic tissue is reviewed and 58 cases added to those previously summarized, bringing the total reported to date to 370.

2. The frequency of occurrence in the different parts of the gastrointestinal tract is stated.

3. A case of aberrant pancreatic tissue in the wall of the stomach, appearing as a polyp on roentgen-ray examination, and removed without relief of the gastrointestinal symptoms, is presented.

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instances, especially in the earlier reported cases, the diagnosis may be questionable. Table 2 gives the distribution in the various locations as found by Poppi in his review. In comparing this with the distribution as found by Hunt and Bonesteel,<sup>33</sup> as given in table 1, we note that these authors found, in addition

TABLE II  
Distribution of Aberrant Pancreatic Tissue in the Cases Reviewed by Poppi in 1935

Stomach	80	Diverticulum (not located)	1
Duodenum	84	Umbilical fistula	1
Duodeno-jejunal angle	2	Mesentery	3
Jejunum	57	Omentum	4
Ileum	10	Splenic capsule	1
Small intestine (not located)	6	Spleen	1
Diverticulum of stomach	3	Gall-bladder	3
Diverticulum of duodenum	5	Cystic duct	1
Diverticulum of jejunum	1	Gastro-colic ligament	1
Diverticulum of ileum	8	Transverse mesocolon	1
Meckel's diverticulum	9	Location questionable	16
Diverticulum of small intestine (not located)	2	Total cases	300

TABLE III  
Cases of Accessory Pancreas Recorded in the Literature Since Poppi's Review in 1935

Year	Author	Stomach	Diverticulum of duodenum	Duodenum	Meckel's Diverticulum	Jejunum	Ileum	?	Total
1932	Picena, J. P. <sup>36</sup> *					1			1
1933	Ayzenberg, A. A. <sup>37</sup> *	1							1
1933	Ross, K. <sup>28</sup> *						1†		1
1934	King, E. S. J. and McCallum, P. <sup>31</sup> *	4							4
1934	Ugelli, L. <sup>38</sup> *	1		2		2			5
1934	Best, R. R. <sup>32</sup> *			2					2
1934	Nishirvo, T. <sup>39</sup> *							1	1
1935	Branch, C. D. and Gross, R. E. <sup>34</sup> *	3	1	9	6	4	1		24
1935	Ciceri, C. <sup>40</sup> *			1					1
1935	Gilbert, R. and Bardet, P. <sup>41</sup> *	1							1
1935	Best, R. R. <sup>42</sup> *	1							1
1935	Azzolini, O. <sup>43</sup> *						1†		1
1936	Stohr, R. and Kogler, K. <sup>44</sup>			1					1
1936	Ugelli, L. <sup>45</sup>		1						1
1936	Nakamura, T. <sup>46</sup>					1			1
1936	Donovan, R. E. and Aguirre, A. C. <sup>47</sup>							1	1
1937	Whiteside, W. C. <sup>48</sup>			1					1
1937	Heilig, W. <sup>49</sup>			1					1
1937	Hill, F. C. and Cohen, L. <sup>50</sup>				1				1
1937	Fanta, E. <sup>51</sup>			1					1
1938	Danzis, Max <sup>52</sup>	1		1					2
1938	Zaslavskiy, L. D. <sup>53</sup>	1							1
1938	Mazzini, O. F. <sup>54</sup>			1					1
1938	Udaondo, C. B. and Jaca, J. A. <sup>55</sup>	1							1
1938	Branscheid, F. <sup>56</sup>			1					1
	Total cases	14	2	21	7	8	3	2	57

\* Not included in previous articles, but recorded in the literature prior to 1935.

† Cases complicated by intussusception.

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## TUMORS OF THE HEART. II. REPORT OF A SECONDARY TUMOR OF THE HEART INVOLVING THE PERI- CARDIUM AND THE BUNDLE OF HIS WITH REMISSION FOLLOWING DEEP ROENTGEN-RAY THERAPY \*

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*Dallas, Texas*

THE first paper of this series<sup>1</sup> included a description of the first reported case of a primary tumor of the heart recognized before death in a patient in whom there was no previous knowledge of tumor elsewhere in the body.† The diagnosis was simple and logical, the same reasoning being applied to a rapidly recurring sanguinous pericardial fluid that has been applied many times to a similar pleural effusion. In that report it was suggested that roentgen-ray therapy might have helped the patient had it been tried early. Curiously enough, as often happens in the practice of medicine, we soon had the privilege of observing a case of a metastatic tumor of the heart which responded promptly to roentgen-ray therapy, though metastases elsewhere resulted in death five months later.

There have been a number of cases of metastatic tumors of the heart which were diagnosed before death,<sup>2</sup> but so far none have been reported showing the effect of deep roentgen-ray therapy on these tumors. In this and doubtless in all the other cases, once the diagnosis was made it seemed useless to try any known form of treatment. However, in our case the patient was in great distress as a result of a very marked pericardial effusion (figure 1), and though we

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From the Baylor University College of Medicine and the Cardiac Clinic of the Baylor University Hospital.

† Solomon Strouse, in his recent article,<sup>2</sup> pointed out that we had erred in giving Pavlovski credit for the first diagnosis of a primary tumor of the heart. It seems that Pavlovski discovered his tumor at the time of autopsy and "reasoned backward from the autopsy protocol and showed how and why these symptoms were produced." Wallace Yater, whose recent excellent article<sup>3</sup> was also in error on this point, restudied these reports at my request and was able to confirm Strouse's statement. Strouse also cited the report by Barnes et al.<sup>4</sup> of a rhabdomyosarcoma of the heart. The tumor was discovered first in the deltoid muscle, and later developments led to the diagnosis of a tumor of the heart. Since this tumor was first discovered outside the heart, their case was regarded as an entirely different diagnostic problem.

tissue consisting of acini, but no island parenchyma; (c) quite large ducts lined with cylindrical cells with pale cytoplasm and normally placed nuclei, with dilatation of some of the ducts. The muscle wall was normal other than for slight diapedesis of polymorphonuclear leukocytes through the walls of arterioles and precapillaries. None of the epithelial elements showed evidence of malignant (atypical) change



FIG. 1. Roentgenogram of stomach showing filling defect at the pars pylorica, suggestive of a polyp, with a central fleck of barium in the ostium.

(figures 2 and 3). Pathological diagnosis: developmental anomalies (aberrant pancreatic tissue in submucosa; dilated ducts and ectopic intestinal type gastric mucosa); low grade chronic inflammatory reaction."

The patient made an excellent recovery from his operation and for a short time seemed to be free of all symptoms. This, however, did not last long; the same symptoms returned and have been present ever since. It is now evident that the accessory pancreas did not cause the gastrointestinal symptoms in this case.

#### SUMMARY

Aberrant pancreatic tissue may occur at any part of the gastrointestinal tract, and occasionally elsewhere. The most frequent sites are the duodenum, stom-



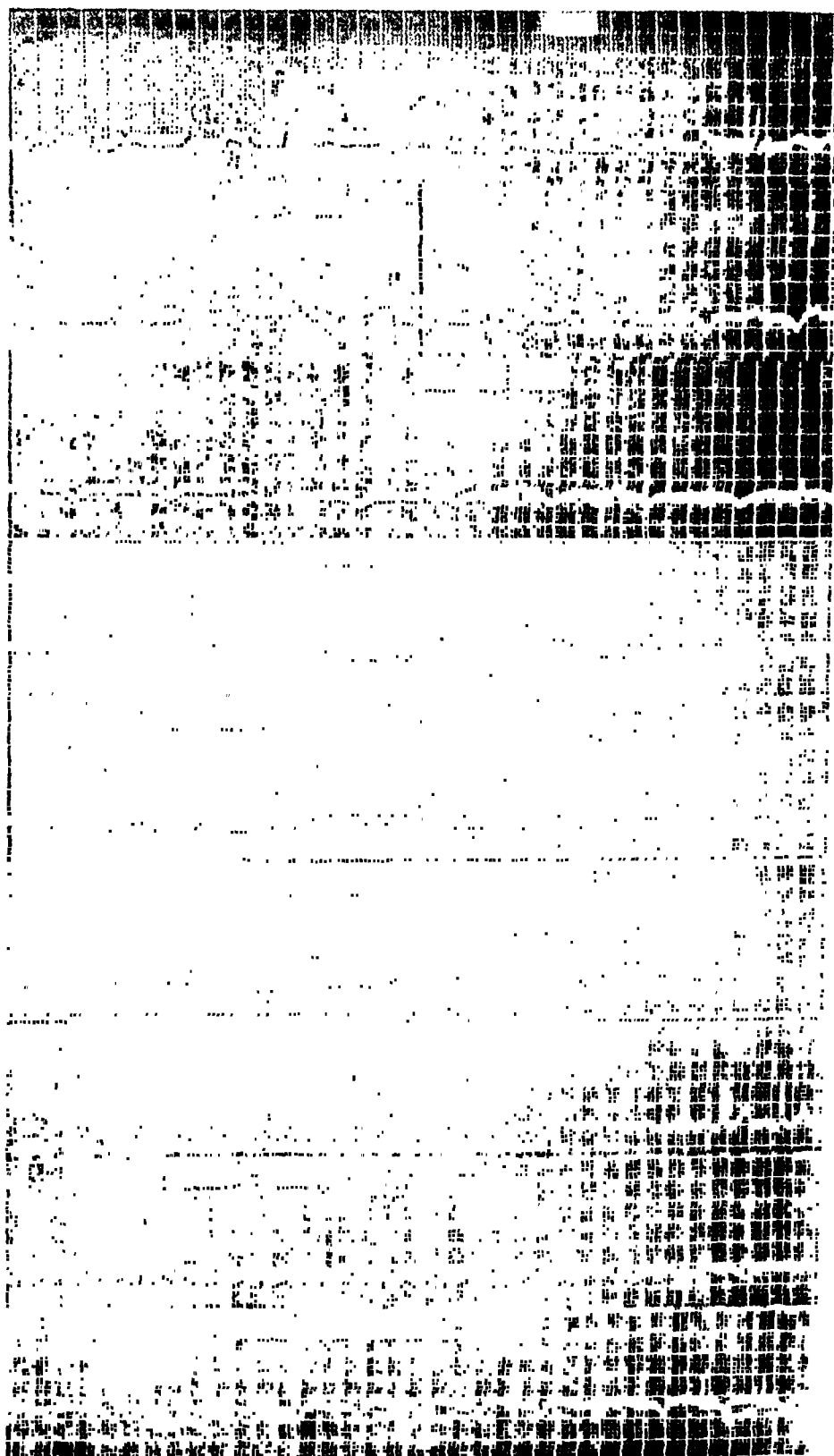


FIG. 2.

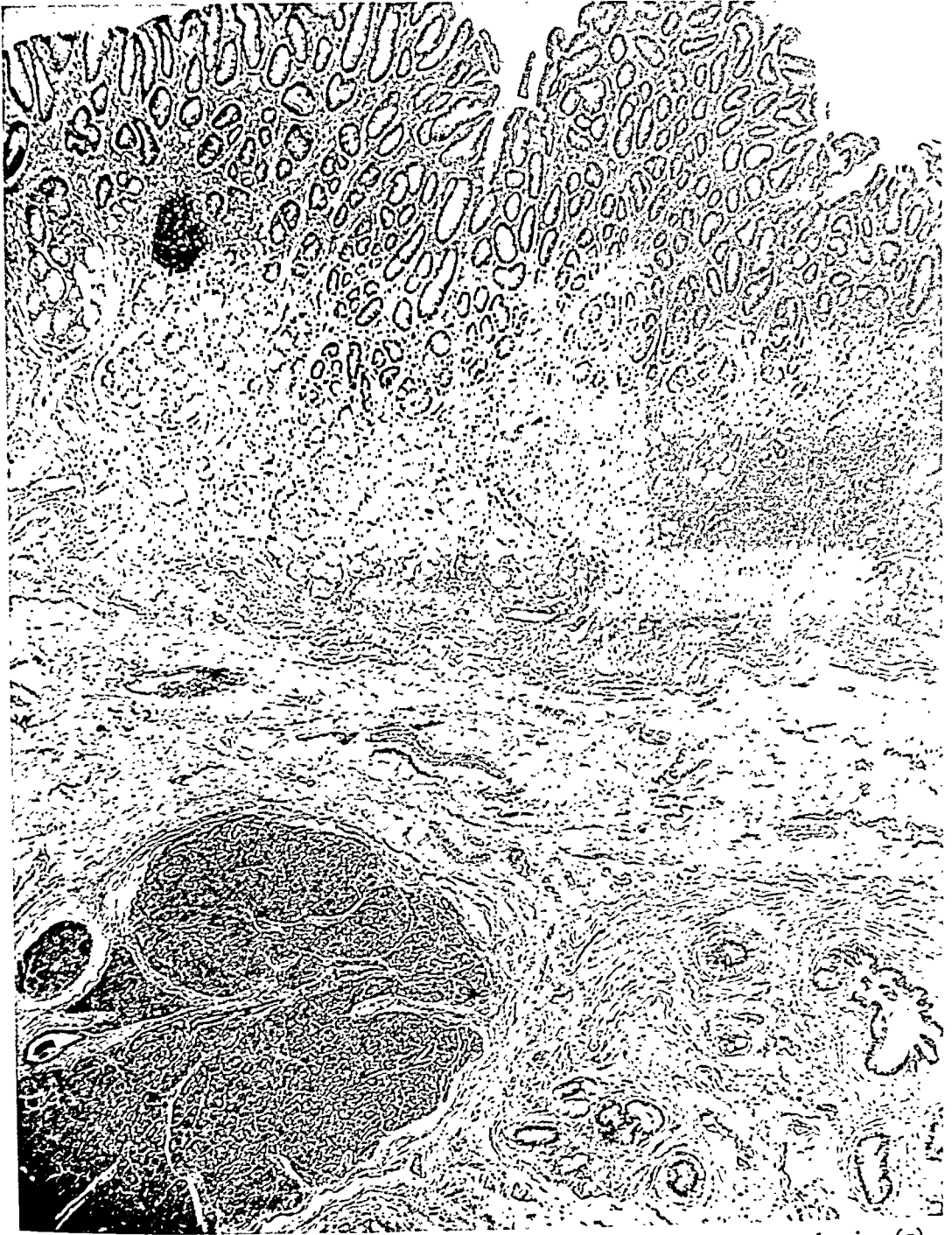


FIG. 3. Photomicrograph of mucosal and submucosal layers through mass, showing (a) intestinal type gastric mucosa, (b) masses of pancreatic acini in the submucosa, and (c) dilated ducts. (Army Medical Museum, No. 67778, Acc. No. 60222.)

therapy, and the subsequent death with mediastinal tumor are adequate proof of the presence of the tumor in the pericardium and in the heart. There was no evidence of tuberculosis, rheumatic fever, nor syphilis. Unfortunately, an autopsy was denied. A most interesting series of electrocardiograms showing the change from complete heart-block, to partial heart-block, to normal mechanism

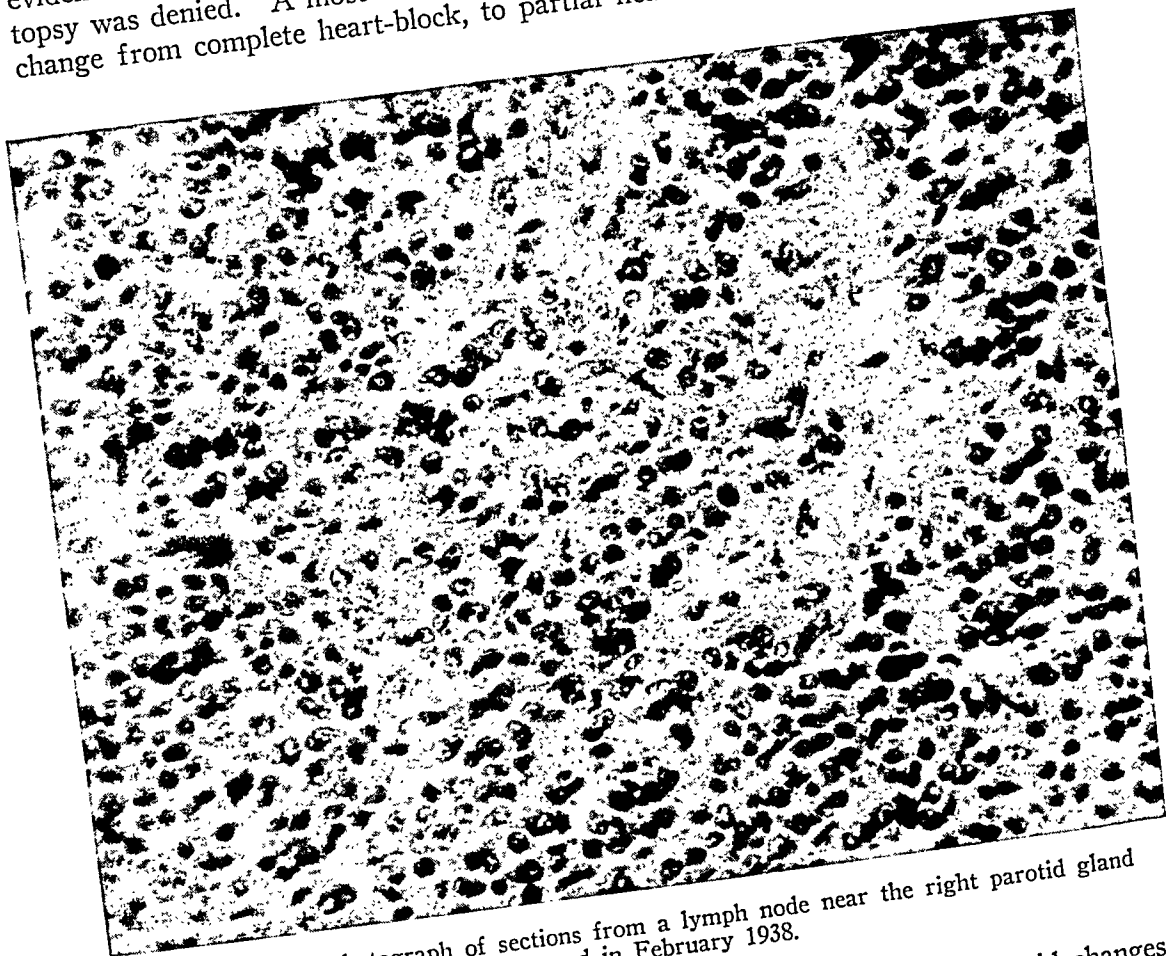


FIG. 3b. Microphotograph of sections from a lymph node near the right parotid gland removed in February 1938.

is included in this report (figure 2). The tracings also show the rapid changes in T-waves, etc., associated with the disappearance of the pericardial effusion. These T-wave changes were not due to the small amount of fluid aspirated from the pericardial sac, as the changes did not occur until 10 days later. In order to show these changes more clearly, a tracing was made almost every day, before and after the treatment, until the mechanism returned to normal. A study of these daily tracings shows that the first change from complete dissociation to 2:1 block occurred on April 14, 1938, nine days after roentgen-ray treatment was started, and that the return to normal mechanism was first recorded on May 11, 1938, 36 days after the onset of roentgen-ray therapy (figure 2). Lead IV was taken each time but was omitted from this figure for the sake of brevity, as it showed the usual upright T-waves and did not change.

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Physical examination at this time showed a well nourished and developed, highly intelligent young man. The blood pressure was 118 systolic and 82 diastolic, temperature 100.2° F., pulse 90, respiration 20. He had a large bone defect in the right side of his head and a scar over the parotid area. There was slight cyanosis of the lips, and in a half reclining position he showed that most characteristic sign of pericardial effusion, distention of the veins of the neck, in a patient able to lie flat in bed comfortably. There was some widening of the cardiac area of dullness and slight but very definite muffling of the heart sounds. The lungs were clear, and the liver and spleen were not palpable; there was no dependent edema.

He was removed to the Baylor Hospital where about 50 c.c. of fluid were aspirated from his pericardial sac. No organisms were present in the fluid and the culture showed no growth after two weeks. The cell count was 16,150 per cu. mm. The fluid did not coagulate on standing. This fluid was carefully centrifuged for a long period and the sediment imbedded in paraffin. Sections of this were made and stained with hematoxylin, and eosin, and also with Wright's stain. These cells were studied by Dr. J. M. Hill, and Dr. George T. Caldwell, Professor of Pathology, Baylor University Medical School, whose report follows:

"Microscopic examination of sediments from pericardial fluid shows numerous peculiar cells of a wide variety of type. These cells vary greatly in character. First of all we find numerous lymphoid cells, moderate numbers of mononuclear cells and a few eosinophiles. The most interesting feature, however, is the presence of fairly numerous, rather large hyperchromatic cells, sometimes having fairly prominent nucleoli. We occasionally find mitotic figures in these cells. There are also a few scattered giant cells, sometimes appearing multilobed and sometimes multinucleated. No definite groupings of these abnormal cells are seen."

These slides, as well as the sections from the original tumor and from the metastatic tumor from the lymph node in the region of the parotid, were submitted by one of us (S. A. S.), on May 5, 1938, to Dr. S. B. Wolbach, Professor of Pathology of Harvard University Medical School. He stated that the cells in the pericardial fluid were unquestionably tumor cells, doubtless the same as those of the original tumor, and he expressed the opinion that the tumor was a type of myeloblastoma probably arising in the medullary portion of the frontal bone (figure 3).

The other laboratory studies were not very significant. The Wassermann was negative. The blood count was: hemoglobin 100 per cent or 15.3 gm., red blood cells 4,950,000, white blood cells 5,480, with 82 per cent polymorphonuclear cells (13 band forms), 17 per cent lymphocytes and one eosinophile. The urine was quite normal, with a specific gravity of 1.022.

The tumor had shown great sensitiveness to roentgen-ray therapy, so we had reason to believe that we could relieve the symptoms of the pericardial effusion by resorting to this form of treatment. The patient was referred to Dr. C. L. Martin, of Baylor Hospital, who gave him daily exposures to roentgen-rays, by a modified Coutard technic, for two weeks starting on April 5, 1938.\*

The changes in the electrocardiograms before and after treatment are very well shown in figure 2. A complete heart-block is present on the tracing taken on April 4, 1938, as well as an inversion of T<sub>2</sub> and T<sub>3</sub>, and a diphasic T<sub>1</sub>. The tracing of April 20, 1938, shows typical 2:1 block and the reversion toward normal T-waves. The tracing of May 11, 1938 shows the return to the normal mechanism and normal T-waves. The roentgen-ray of the heart taken on April 4, 1938, shows a diameter of the heart of 18.8 cm.; on April 20, 1938, the diameter was 15.9 cm., and on June 30,

\* Between April 7, 1938, and April 20, 1938, the patient received 1800 r measured in air, delivered to each of two areas measuring 15 cm. on a side laid out over the anterior and posterior aspects of the cardiac region. The daily dose was 300 r and the factors were 200 Kv., 25 Ma., a filter of 3/4 mm. of copper, and 1.0 mm. of aluminum, and a target skin distance of 50 cm. The output of the tube was 40 r per minute.



FIG. 1. This clearly shows the changes in the size of the heart shadow before and after roentgen-ray treatment. The cardiac diameter on April 5, 1938, was 18.8 cm., on April 20, 1938, 15.9 cm., and on June 30, 1938, 15.3 cm. The last film shows the beginning of the recurrence in the mediastinum.

## SUMMARY

This is a report of a malignant tumor, invading the pericardium and the septum of the heart, which was treated by deep roentgen-ray therapy. There was strong evidence that the tumor was largely destroyed and that the function of the heart was not impaired by the treatment. The roentgen-ray films of the heart, the electrocardiographic tracings, and the microphotographs of the tissues are presented. They show the interesting sequence of events following roentgen-ray treatment of the tumor in the heart.

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felt sure he would not recover entirely from his tumor, we hoped that the roentgen-ray treatment would relieve the symptoms of the pericardial effusion. Our hopes of helping him were dampened by the presence of a complete heart-block shown in the electrocardiogram, clearly indicating deep invasion of the heart by the tumor. However, the result was extremely gratifying. The effu-

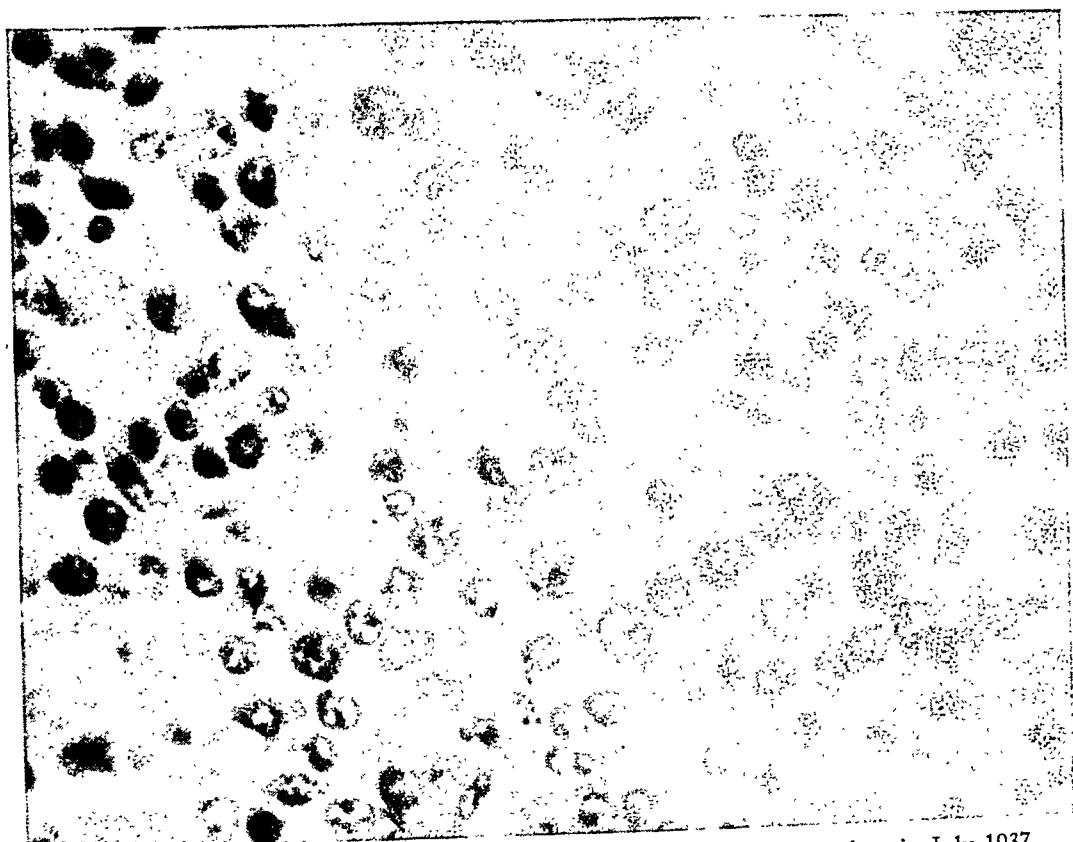


FIG. 3a. Microphotograph of sections of tissue removed from the cranium in July 1937.

sion completely disappeared and, curiously enough, the complete heart-block (figure 2) also disappeared, which led us to believe that at least a portion of the tumor in the intraventricular septum had been destroyed. The man was able to get out of bed and return to his regular work for about two months, and expressed extreme gratitude that he was given this respite. He subsequently died with the typical symptoms and findings of extensive secondary mediastinal tumor. Tissue sections of the original tumor, which arose in his skull or dura, and the first metastatic lesion in the neighboring lymph node were studied (figure 3). Cells typical of this tumor were found in the pericardial fluid (figure 3). The presence of these cells in the aspirated pericardial fluid, plus the immediate complete disappearance of the fluid and of the a-v block following roentgen-ray

FIG. 2. Electrocardiographic tracings showing the change from complete a-v block to 2:1 block, to normal mechanism, and the changes in  $T_1$  and  $T_2$ . The change from complete block to 2:1 block first appeared on April 14, 1938, and the T-waves became upright about the same time. The depression in the S-T intervals in Leads I and II are probably too small to be of significance.



## SUMMARY

This is a report of a malignant tumor, invading the pericardium and the septum of the heart, which was treated by deep roentgen-ray therapy. There was strong evidence that the tumor was largely destroyed and that the function of the heart was not impaired by the treatment. The roentgen-ray films of the heart, the electrocardiographic tracings, and the microphotographs of the tissues are presented. They show the interesting sequence of events following roentgen-ray treatment of the tumor in the heart.

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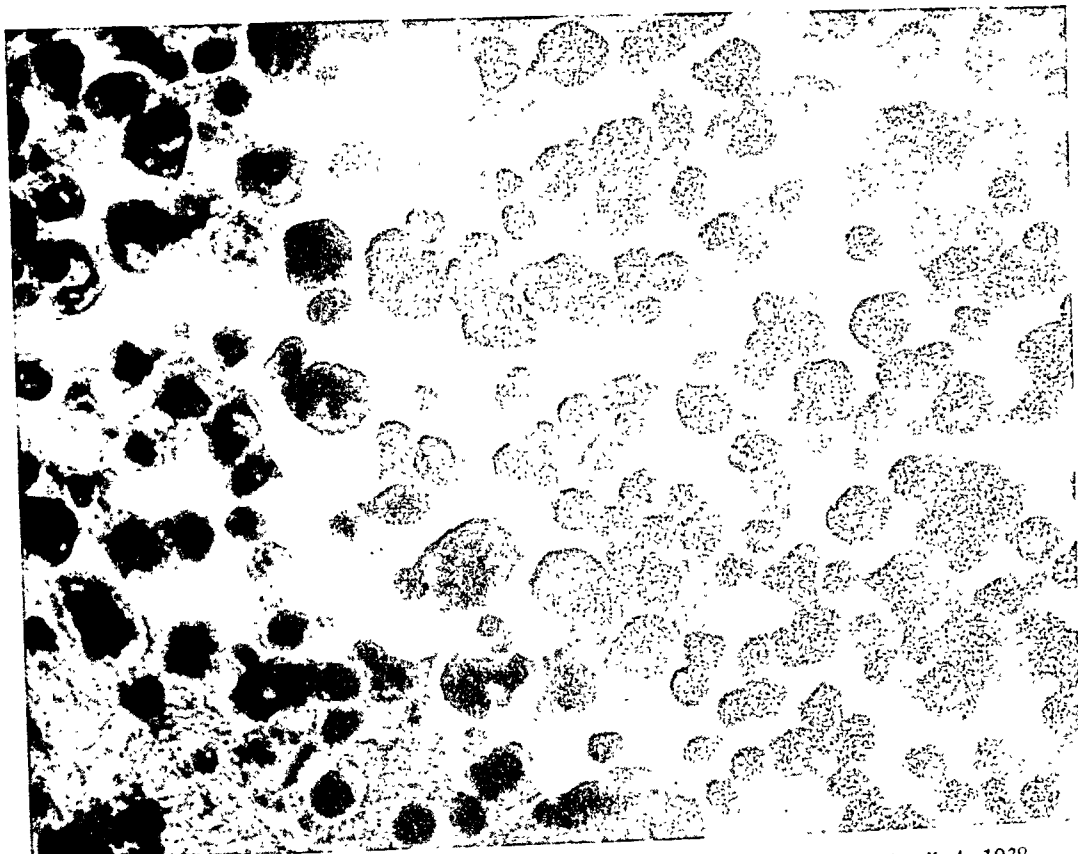


FIG. 3c. Microphotograph of sections of cells in the pericardial fluid April 4, 1938.

#### CASE REPORT

G. R. was a married, Polish Jewish, cotton importer, aged 28, who was seen first by Dr. Howard Aronson on March 15, 1938. He was in bed and complaining of fever, malaise, attacks of nausea, and dyspnea.

This patient gave a history of the development of a tumor over the right parieto-frontal region of his skull in July 1937. In August 1937, Dr. Harry Mock of Chicago, where the patient was living at that time, removed the tumor, including a large bone flap from this area, and then gave him a course of deep roentgen-ray treatment. Dr. Mock thought that the tumor arose from the dura, and microscopic sections (figure 3) were studied by Dr. E. F. Hirsch, who expressed the opinion that the tumor was a dural sarcoma. The patient felt very well until early February 1938, when he developed a recurrence in the region of the parotid gland which Dr. Mock removed; and roentgen-ray treatment was again administered over the region. He improved again and came to Dallas to carry on his work. About March 15 he began to have fever every day, reaching about 102° F. in the afternoon, as well as attacks of nausea and dyspnea. Efforts to determine the cause of the fever were not rewarded with success until a film of the chest was made, at which time the pericardial effusion was found. The lung fields were clear. On reviewing this history we felt certain that we were dealing with a metastatic tumor of the pericardium. Since these metastatic tumors frequently invade the septum, an electrocardiographic tracing was made on our first visit together in his home on April 4, 1938. This tracing (figure 2) showed a complete a-v dissociation which we felt furnished further positive evidence of the presence of the tumor.

may accelerate these crucial problems; the mortality of war is largest among the youthful. There is no end to the list of problems and only a very meager beginning has been made toward their solution. The potentialities of the senescent for service have been barely touched. Accomplishments of such men as Oliver Wendell Holmes, W. H. Welch, Goethe, Edison, Titian, and many others in the evening of their lives are mere indicators of the vast storehouse of latent treasure existent in those so often sneeringly dubbed "old men." The judgment and experience of mature and highly trained minds are invaluable national assets. In times of stress and emergency it is upon the older shoulders that the greatest responsibilities rest. Conservation of such precious resources is a major responsibility of gerontology.

The medical implications of this fundamental shift in the age and character of the national population are many. The remarkable increase in longevity is due largely to improved preventive medicine and effective pediatrics. The saving of life in infancy and childhood, the control of infective diseases such as typhoid fever, smallpox and the like, have made possible the extension of life expectancy. As a consequence, the incidence of the so-called degenerative disorders, or those whose frequency rises sharply in later life, has increased conspicuously. Cardiovascular-renal disease, cancer, diabetes mellitus, arthritis, and cerebral accidents are replacing infective diseases as the most common causes of death. These are all chronic and progressive disorders, usually insidious of onset and silent until disability causes premature arrest of activities. Though we are learning much about therapeutic control of these disorders, honesty compels admission that cure and prevention are desiderata as yet unobtainable.

These disorders are not amenable to mass prevention as are infectious diseases. Preventive medicine must become individualized. Extension to mature adults of the wise pediatric policy of keeping children in the best of health by personal health maintenance programs is necessary if we hope to stem the rising tide of disability among those past the meridian. To be effective in health maintenance, medicine needs more precise methods of evaluating health than are available today. Though accuracy in diagnosis of disease has made immense advance, the mensuration of health is a wholly different problem. We can no longer say that health is the mere absence of obvious disease. Health evaluation involves the measurement of functional reserve capacities. These change with age. Normal is not a fixed point but a variable affected by age. The normal must be known and appreciated before the abnormal can be interpreted intelligently.

Senescence can not be measured by chronologic age. Physiologic age is not synonymous with chronologic age! Physiologic time<sup>2</sup> does not progress uniformly but varies its pace in different individuals, at different periods in the same individuals, and in the aging of different functions and structures. Criteria for the evaluation of physiologic age in man are

<sup>2</sup>. CARREL, A.: Physiological time, *Science*, 1931, lxxiv, 618. DuNoüy, PIERRE: Biological time, 1937, Macmillan, N. Y.

1938, it was 15.3 cm. (figure 1). The last film shows the recurrence of the tumor in the mediastinum.

The patient continued to have the fever, which he had had for three weeks, until the fifth day after roentgen-ray therapy was begun. He had no fever after that until the onset of the terminal episode four months later. The attacks of nausea persisted for about seven days. Roentgen-ray therapy was completed on April 20, 1938, and he was allowed to return to work a few days later. At this time he had no symptoms, but he was advised to refrain from any unusual exertion. He went about his work fairly well until June 21, 1938, when he developed a definite recurrence in the right side of the neck which disappeared soon after the institution of roentgen-ray therapy to this region. A mediastinal invasion was discovered on June 28, 1938, and he returned to Chicago for the duration of the summer, planning to take further treatment there. However, the tumor persisted and increased despite treatment, and the patient died of mediastinal compression on September 27, 1938, in St. Luke's Hospital, Chicago. There were marked dyspnea and extensive edema involving the neck, both arms and hands, and the upper portion of the body.

#### COMMENT

Metastatic tumors of the heart are not very rare, as they occur in approximately 0.5 per cent of cases of malignancy, and they are often easily recognized before death. This is particularly true when a pericardial effusion occurs in a patient with a known malignant tumor, or when such a case shows some form of heart-block in the electrocardiogram. These are the two ways in which the diagnosis has been made most commonly. Occasionally the diagnosis is made by a bizarre appearance of the heart shadow on the roentgen-ray film. The subject of this report had a primary tumor of the skull and both a pericardial effusion, with typical tumor cells in the fluid, and a complete heart-block, as shown in the electrocardiogram. He had a highly malignant tumor, probably a myeloblastoma which arose in the cranium, and which finally caused his death by a mediastinal compression.

He was subjected to deep roentgen-ray therapy according to a modified Coutard technic, with the hope of relieving some of his distress. We were amazed and gratified by the effectiveness of this treatment. The portion of the tumor invading the heart and pericardium must have been largely destroyed by the roentgen-rays, as the effusion vanished, and, to our surprise, the heart-block disappeared leaving a normal cardiac mechanism. As far as we can tell, this did not recur in these areas, though the time for recurrence was short, as the patient died of mediastinal compression about five months later.

Probably the most convincing sign of the efficacy of the roentgen-ray therapy was in the change from complete block to 2:1 block, then to normal mechanism. The change to 2:1 block occurred on the ninth day after the onset of treatment. The change in the T-waves, which probably indicated pronounced decrease in the pericardial effusion, occurred about the same time. This is confirmed by the decrease in the heart shadow on the roentgen-ray film observed on the fifteenth day after treatment.

It is doubtful at the present time that these observations are of any real value to patients with malignant tumors invading the heart. They do prove that the roentgen-rays will destroy tumors deep in the heart without any obvious effect on the function of the heart muscle.

just what problems are being studied and the methods of approach being applied. It is highly probable that many investigations which do not pertain directly to aging will, nevertheless, yield data significant to the science if looked upon from a broad viewpoint. Inquiries regarding studies related to aging are being sent to scientists in the basic biologic sciences as well as to clinical investigators. From the clinical point of view the survey is concerned especially with those studies dealing with health evaluation, mensuration of functional capacities as criteria of physiologic age, and those diseases whose incidence rises sharply in later life.

Critical analysis of the information elicited by such a survey may be expected to serve several valuable purposes. It should assist in bringing together in closer coöperation investigators interested in related problems, especially when widely divergent methods of approach are being utilized. The survey will likewise emphasize the urgent need for greatly augmented support for significant studies of these vitally important problems of senescence. The broad and general pattern of the problems being investigated will undoubtedly reveal a number of neglected "blank spots" which may justify special emphasis in the future. Analysis of the data of the survey will also be an invaluable aid in formulating future research programs.

E. J. S.

## EDITORIAL

### GERONTOLOGY

GERONTOLOGY, which is the science of aging, is no longer of mere academic interest, but presents innumerable significant questions urgently demanding study and solution. Aging is a continuous biologic process which commences immediately upon the creation of a new individual and continues until death. Therefore, gerontology crosses the pathways of thought of all biologic sciences and presents problems at all ages. In this, gerontology differs conspicuously from geriatrics which has been defined as "that branch of medical science which treats of the *aged* in their physiologic and pathologic relations." Thus geriatrics is concerned with the consequences of senescence, the end result of senility, whereas gerontology includes in its domain of thought the processes of involution and senescence from conception onward.

Why have the problems of aging become so urgent? Surely aging is no recent phenomenon! The ancient Greeks were much concerned with the philosophy of the aged and Cicero orated with both passion and compassion upon the problems of the senescent. But the aged then were few and far between; careful estimates place the average duration of life of the ancient Roman citizen at from 20 to 30 years. Life expectancy increased slowly for many centuries and it is only in the last fifty years or so that conspicuous changes have occurred. In 1850 life expectancy in New England was but 40 years. By 1900 longevity in the United States had risen to 48 years, but since then the advance has been dramatic. By 1930 it had increased to over 60 years of age. The studies of Dublin<sup>1</sup> reveal the following significant figures: In 1900, 46 per cent of the total population of the United States was under 20 and but 17 per cent exceeded 45; in 1940 the youth under 20 are 34.7 per cent and those over 45 constitute 26.5 per cent of the population. By projection, it is conservatively estimated that in 1980, only forty years hence, only 26 per cent of the population will be youths under 20 and that those over 45 will include more than 40 per cent of our people.

The nation is aging rapidly. The virile, violent, but short-lived days of pioneering are largely passed. The future holds promise of profound changes. Urgent and unanswered problems arise in economic, political, sociologic, and psychiatric fields as well as in medicine. The children of today will be the elderly of tomorrow. The direction of some of the problems is already indicated. The clamor of the aged for economic security is heard throughout the breadth of the land. Even fantastic schemes such as those of Townsend are fanatically advocated. The problem of employment of older men demands serious attention. The grim specter of war

<sup>1</sup> DUBLIN, L. I.: Chapter 6 in COWDRY's "Problems of aging," 1939, Williams & Wilkins Co., Baltimore.

*Obesity and Leanness.* By H. R. RONY, M.D. 300 pages; 24 × 15 cm. Lea and Febiger, Philadelphia. 1940. Price, \$3.75.

A good book. The controversies in this complicated aspect of medicine are critically probed, in a factually explicit, even reportorial style. A generous sprinkling of the author's own studies is checked against the findings of others.

Beginning with an impartial evaluation of the problems and data of fat metabolism, the rôle of adipose tissue in the cycle is considered. Caloric balance as the sole cause of obesity is scouted. Dynamic and static phases of weight production are urged. The chapter on lipophilia is the best discussion of that concept this reviewer has seen, and a chapter on the nervous system and its relation to obesity is particularly good. Appetite and hunger are stressed rather more than seems justified, and the discussion of the intermediary metabolism is not sufficiently documented.

The references are good, and the chapter résumé particularly helpful. Emphasis on follow-up is well placed. With the avitaminoses assuming the proportions of a public health problem, this book should be required reading for all concerned with dietary and metabolic problems.

C. A.

*Diseases of the Digestive System in Food Allergy.* By JOSEF SMUL, M.D. 219 pages; 22.5 × 15 cm. Medical Library Co., New York City. 1940. Price, \$3.50.

This book is a collection of erroneous statements presented with complete solemnity. It is not only completely valueless but is actually potentially dangerous in that, in such conditions as gastrointestinal malignancies, it gives far-advanced findings as diagnostic criteria.

H. M. B.

*The Diagnosis and Treatment of Diseases of the Esophagus.* By PORTER P. VINSON, B.S., M.A., M.D., D.Sc., F.A.C.P. 224 pages; 23 × 15 cm. Charles C. Thomas, Springfield, Illinois. 1940. Price, \$4.00.

This textbook devoted entirely to diagnosis and diseases of the esophagus is an excellent contribution to the literature on this subject. The value of esophagoscopy as a means of diagnosis and treatment is stressed. The technic for its use is clearly described. The importance of studying related general symptoms before a diagnosis is made is emphasized.

Hysterical dysphagia, cardiospasm, esophagitis, diverticula, tumors and foreign bodies are carefully considered. A great deal of attention is given to the diagnosis and treatment of strictures of the esophagus. The technic of dilatation is well illustrated. Cancer of the esophagus is thoroughly discussed and methods of treatment outlined. The internist will find this book very valuable as a reference.

E. A. L.

*Obstetrics and Gynecology.* By the Departmental Staff of the University of Chicago and other contributors. Edited by FRED. L. ADAIR, M.A., M.D., F.A.C.S. Vol. I: 1000 pages; Vol. II: 1031 pages, 24 × 15 cm. Lea and Febiger, Philadelphia. 1940. Price, \$20.00.

This work represents the combined judgment of the members of the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-in Hospital, because no names are associated with the individual chapters. The Editor considers obstetrics and gynecology one specialty, advocates the combination of these two fields, and has arranged the subject matter with this concept in view. He states that since obstetrics is of major importance, the larger portion of the work is devoted

## EDITORIAL

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## COLLEGE NEWS NOTES

### A. C. P. COMMITTEES AND REGENTS TO MEET

By direction of the President, the various Committees and the Board of Regents of the College will meet at the College Headquarters in Philadelphia, December 14-15, 1940, for the transaction of the regular mid-year business.

Among many important matters to be considered will be the statement of operation, the adoption of 1941 budgets, election of candidates to membership, the selection of the recipient of the John Phillips Memorial Award for 1941, adoption of the program of postgraduate and refresher courses for 1941 and final arrangements for the Twenty-fifth Annual Session of the College in Boston.

### GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members, recently received, are gratefully acknowledged. It is with particular gratification and deep appreciation that the donation of so many books by College members is here recorded.

The inspiration for the forming of a library of books, of which members of the College are the authors, grew out of an act of courtesy and thoughtfulness of a few years back when a member presented his autographed book to the American College of Physicians. The Library, in a sense, is intended to be a *memorial library* to our members. A general medical library, other than one of this character, would scarcely be justified at the College Headquarters, due to the availability of so many general medical libraries in Philadelphia. The College library of books has a growing interest and increasing value and will have a deeper sentiment as the years pass by.

Fellows of the College constitute a group of the most productive medical men of America. Books they have written occupy in many institutions a forefront position in American medical literature. Authors who are members of the College are especially invited to donate autographed copies of their books to this Library. Gifts will be promptly acknowledged both personally and through this journal. Appropriate bookplates, giving date of receipt and name of donor, are attached, and the books are properly indexed and added to the Library.

#### *Books*

- Dr. Joseph H. Barach, F.A.C.P., Pittsburgh, Pa., "Diabetes—Self Help for the Diabetic";
- Dr. David P. Barr, F.A.C.P., St. Louis, Mo., "Modern Medical Therapy in General Practice," Volumes I, II, and III;
- Dr. Albert G. Bower (Associate), Glendale, Calif., "Communicable Diseases for Nurses";
- Dr. Linn J. Boyd, F.A.C.P., New York, N. Y., "Cardiovascular Diseases—Their Diagnosis and Treatment" and "Clinical Electrocardiography";
- Dr. William B. Castle, F.A.C.P., Boston, Mass., "Lectures on the Anaemias and Vitamin Deficiencies";
- Dr. Russell L. Cecil, F.A.C.P., New York, N. Y., "A Textbook of Medicine by American Authors," 5th edition;
- George Washington University School of Medicine, Washington, D. C., "Studies from the School of Medicine, George Washington University, for 1939-1940";
- Dr. Sigmund S. Greenbaum, F.A.C.P., Philadelphia, Pa., "Diseases of the Mouth and Their Treatment," 2nd edition;

urgently needed by clinical medicine. Undoubtedly no single criterion can ever suffice but physiologic studies intended to reveal depreciation in functional capacities may prove illuminating. The years from 40 to 60 are probably the most significant period for the application of prophylactic geriatrics which has for its objective not the prolongation of life beyond the basic limits set by species inheritance, but the maintenance of health and usefulness until senility really equals infirmity. Much more can be accomplished with the aging than for the aged. The two major obstacles are lack of accurate knowledge and man's perversity in ignoring prophylactic measures if they involve the slightest effort on his part. These obstacles are not insurmountable. The science of medicine can remove the first and the art of medicine can overcome the latter.

Gerontology, however, encompasses far more than the questions engendered by clinical study of "normal" aging in man and the disorders characteristic of later life. Improvement of clinical practice in prophylactic geriatrics is dependent largely upon advances in knowledge concerning the fundamental biologic processes of senescence. All living things age. Critical data anent the phenomena of aging may, therefore, be derived from studies of many diverse forms. The disciplines of botany, bacteriology, genetics, zoölogy, and all the many methodological subdivisions of the biological sciences are concerned with aging. There is great need for delineation and precise description of the structural, biochemical, and physiologic changes which constitute normal involution<sup>3</sup> or senescence. Paralleling such descriptive studies are needed investigations into the etiologic and pathogenetic factors involved. Experimental attempts at retarding or accelerating senescence may be expected to yield information illuminating the underlying mechanisms of aging. Though it is obvious that growth and tissue metabolism are greatly influenced by age, there is almost no precise information as to the manner of these relationships. Basic knowledge here may prove to be a key to the riddle of cancer. In brief, gerontology seeks to learn just what aging is, what it does, why it occurs, and what factors determine its rate and character.

In view of the extent and importance of this relatively unexplored science, it is gratifying to learn that the National Institute of Health, which is the research division of the U. S. Public Health Service, is now organizing and developing a new unit for research in gerontology. Though there are many scientists actively and significantly attacking the problems of aging, there has been no previous centralizing agency. The breadth of the field and the multiplicity of disciplines involved have prevented any comprehensive correlation of the many diverse investigations. Therefore, the first service this new unit is undertaking is to conduct a survey of the present trends of active and contemplated investigations into the problems of aging in American scientific institutions. This survey is intended to ascertain

<sup>3</sup> WARTHIN, A. S.: *Old age: The major involution*, 1929, Paul B. Hoeber, Inc., N. Y.

AMERICAN BOARD OF DERMATOLOGY AND  
SYPHILOLOGY:

C. Guy Lane, M.D., Secretary  
416 Marlboro St.  
Boston, Mass.

AMERICAN BOARD OF PATHOLOGY:

F. W. Hartman, M.D., Secretary  
Henry Ford Hospital  
Detroit, Mich.

AMERICAN BOARD OF PEDIATRICS:

C. A. Aldrich, M.D., Secretary  
723 Elm St.  
Winnetka, Ill.

AMERICAN BOARD OF PSYCHIATRY AND  
NEUROLOGY:

Walter Freeman, M.D., Secretary  
1028 Connecticut Ave., N. W.  
Washington, D. C.

AMERICAN BOARD OF RADIOLOGY:

B. R. Kirklin, M.D., Secretary  
102 Second Ave., S. W.  
Rochester, Minn.

Oral Examination, Chicago, December 6-7, 1940.

Applicants classified in Group B take both the written and oral examinations; applicants classified in Group A take the oral examination only.

Cleveland, June, 1941, in connection with the meeting of the American Medical Association.

New York City, March 30-31, 1941, immediately following the Region I meeting of the American Academy of Pediatrics.

Chicago, May 18, 1941, immediately following the Region III meeting of the American Academy of Pediatrics.

New York City, December 18-19, 1940.

Cleveland, June, 1941, in connection with meeting of the American Medical Association.

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On September 18 Dr. Edward L. Bortz, F.A.C.P., was inducted as President of the Philadelphia County Medical Society. Dr. Rufus S. Reeves, F.A.C.P., was the retiring President and Dr. Louis H. Clerf, F.A.C.P., is the President-Elect.

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The 1940 Graduate Fortnight of the New York Academy of Medicine was held in New York City October 14-25. The subject of this Fortnight was "Infections." Dr. Charles F. Tenney, F.A.C.P., New York, was Chairman of the Committee on Panel Discussions, and Dr. F. Warner Bishop, F.A.C.P., New York, was Chairman of the Committee on Hospital Clinics.

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Dr. Christopher C. Shaw (Associate), Bellows Falls, Vt., has been commissioned a Lieutenant Commander in the Medical Corps of the United States Naval Reserve.

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Dr. John F. Kenney, F.A.C.P., Pawtucket, R. I., has been appointed a member of the new Basic Science Board for the State of Rhode Island for a term of two years.

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Among those who have been appointed to the Territorial Committee on Medical Preparedness by the Puerto Rico Medical Association, to work in coöperation with the state representative of the Committee on Medical Preparedness of the American

## BOOK REVIEWS

*Endocrine Therapy in General Practice.* By ELMER L. SEVRINGHAUS, M.D., F.A.C.P. 192 pages; 21 × 15 cm. The Year Book Publishers, Inc., Chicago. 1938. Price. \$2.75.

This brief and concise book is written for the man in general practice. The author endeavors to explain the rationale in the present use of endocrine substances and to point out what can be expected from them. The individual products of the pharmaceutical houses are recorded by name and the recommended dose given. This in itself should prove of help to practicing physicians, many of whom are besieged by the detail men to such an extent that they are apt to become bewildered.

As is stated in the preface this work is in no sense encyclopedic in content. Nevertheless both gynecologists and endocrinologists can derive much benefit from reading it. For those who do not feel that the material presented is sufficiently comprehensive references for further reading are given at the end of many of the chapters. The book contains many photographs of patients. These illustrate the changes in bony contour and fat disbursements that occur with endocrine disturbances.

L. B.

*Dermatologic Allergy; Introduction in the Form of a Series of Lectures.* By MARION B. SULZBERGER, M.D. 540 pages; 23.5 × 16 cm. Charles C. Thomas, Springfield, Illinois. 1940. Price, \$8.50.

The author holds a unique position in the field covered by this volume. He has greatly influenced the current attempt to classify and arrange those skin diseases known or believed to be the result of allergic processes. Dr. Sulzberger reveals a profound knowledge of his subject, a knowledge which combines a wide dermatologic experience with a thorough understanding of the subject of allergy.

The material is presented as a series of lectures, which are apparently those delivered by the author in his teaching. Usually, in the opinion of the reviewer, this is not the best way of arranging a text, but it serves Dr. Sulzberger's purpose satisfactorily because so much of his material has to do with a subject that is in a state of flux and consequently must be presented in a discursive and non-dogmatic fashion.

His use of the word "allergy" as an all inclusive term, including increased reactions of specific sensitivity and the decreased reactions of immunity, is at variance with the current use of the term but his arguments in favor of this use are quite persuasive.

The lecturer seeks to show the similarity between sensitivity resulting from infection and that resulting from non-living materials and does it very well. He differentiates between eczematous or contact type reactions, urticarial responses and those reactions resulting from sensitivity to infection.

He discusses in detail allergy to tuberculin, to fungi, to syphilis, to miscellaneous infections and to drugs in a clear and most interesting manner.

There are many who do not entirely agree with the author's conception of dermatologic allergy, but none ignore him. All the workers interested in allergy or dermatology have some opinion in the matter, being either for or against his conception.

The book is unique in its field and has served to crystallize a subject that has heretofore been vague in its outline. The reviewer feels justified in recommending it highly to those interested in this phase of medicine.

H. M. B.

Dr. Aura J. Miller, F.A.C.P., Louisville, Ky.—“Epithelioma of the Labia, with Discussion of Methods of Treatment.”

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Dr. J. Howard Holbrook, F.A.C.P., College Governor for Ontario, Hamilton, was chosen President-Elect of the Canadian Tuberculosis Association at their annual meeting in Montreal in June.

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The British Columbia Medical Association held its annual meeting in Nelson, B. C., September 9–11. Among the speakers at this meeting were:

Dr. Albert M. Snell, F.A.C.P., Rochester, Minn.—“Deficiency States and Their Treatment” and “Problems Presented by the Jaundiced Patient”;  
Dr. George H. Anderson, F.A.C.P., Spokane, Wash.—“Hyperventilation Syndrome.”

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The American Psychiatric Association held its second regional postgraduate institute at the Central State Hospital, Lakeland, Ky., September 23 to October 5, in coöperation with the division of hospitals and mental hygiene. Among the lecturers at this institute were Dr. S. Spafford Ackerly, F.A.C.P., Louisville, Ky., Dr. Lawrence Kolb, F.A.C.P., Washington, D. C., and Dr. Edward G. Billings (Associate), Denver, Colo.

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The 35th annual meeting of the Tri-State Medical Society was held in Shreveport, La., September 25–26. Among the guest speakers at this meeting were:

Dr. George W. Parson, F.A.C.P., Texarkana, Ark.—“Interesting Cases of Tular-emia”;  
Dr. Homer E. Prince, F.A.C.P., Houston, Tex.—“Asthma—Practical Considerations”;  
Dr. Silas C. Fulmer (Associate), Little Rock, Ark.—“Diagnosis of Heart Disease.”

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Among the guest speakers at the 18th annual clinical conference of the Kansas City Southwest Clinical Society, held in Kansas City, Mo., September 30 to October 3, were:

Dr. John T. King, F.A.C.P., Baltimore, Md.—“Relation Between Coronary Disease and Hypertension”;  
Dr. Fred M. Drennan, F.A.C.P., Chicago, Ill.—“Diagnosis and Interpretation of Clinical Findings in Peptic Ulcer”;  
Dr. Thomas Fitz-Hugh, Jr., F.A.C.P., Philadelphia, Pa.—“Interrelationship of Cholelithiasis and Coronary Artery Disease”;  
Dr. James S. McLester, F.A.C.P., Birmingham, Ala.—“The Part Played by the Vitamins in Human Metabolism”;  
Dr. James G. Carr, F.A.C.P., Chicago, Ill.—“Prognosis in Cardiac Disease”;  
Dr. Clifford J. Barborka, F.A.C.P., Chicago, Ill.—“Management and Treatment of Obesity.”

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Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., spoke on problems in gastroenterology at a meeting of the Ninth Councilor District in Marshfield, Wis., July 11.

to that field. He also states that the work is not primarily intended for a reference, but designed for the medical student and the practitioner of obstetrics and gynecology. The reviewer is of the contrary opinion because of the size of the work, the statistical data presented, the numerous charts, the historical chapters, and chapters correlating obstetrics and gynecology with other fields, all of which stamp it as a reference work; and because medical students will probably use such a work as a reference rather than as a text. In addition, the usual text does not attempt to give such a full account of the medical, social and economic importance of human reproduction as is found here. The chapter on obstetric morbidity and mortality establishes the work as a reference in the opinion of the reviewer. Principles are stressed and the fields of obstetrics and gynecology and biology and medicine in general are correlated.

The material dealing with pathology throughout the work is unusually well presented, and accompanied by excellent illustrations. For the practitioner there is a chapter on obstetrics in the home which includes valuable suggestions on the diagnosis and management of the more dangerous complications. In a work presented as a text the reviewer was surprised to find so little space devoted to the common obstetrical and gynecological operations with very few illustrations of some of the common procedures with which the student and practitioner must be familiar.

Interesting data relative to history, laws and customs are to be found. There is a timely chapter on the relationship of infection and immunity to reproduction. Biology and problems of reproduction and the relationships of the basic sciences and clinical medical sciences to obstetrics and gynecology are fully considered. Of special interest to readers of this journal is the chapter on internal medicine in relation to obstetrics and gynecology, in which the field is well covered. There is a valuable chapter on puerperal infection with instructive case histories appended. There are seven chapters devoted to the newborn and to pediatrics. The chapter on roentgen diagnosis in obstetrics and gynecology is interesting and well illustrated.

The volumes are large and each has a convenient ribbon bookmark. There is an index for both volumes at the end of each. The type is clear and the style pleasantly readable. The illustrations are excellent and for the most part original though rather few in number. There is a valuable appendix concerning dietetics, laboratory methods, and vital statistics. The list of references occupies 25 pages and is found in volume 2. The references are arranged alphabetically by author, and frequently only the specific journal reference is given with no title of the article. This does not appear to the reviewer as practical and efficient a method as that in which they are given under subject headings or at the end of each chapter.

The work represents a significant contribution to obstetrics and gynecology and the growing tendency toward the combination of these fields for the purpose of "improved service, teaching and research." This is an elaborate work and the Editor and his associates should be congratulated upon the successful completion of so great a task. It undoubtedly is a work which every practitioner of obstetrics and gynecology will find profitable.

J. E. S.

Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill.—“The Primary Tuberculous Infection in Adults”;

Dr. Reginald Fitz, F.A.C.P., Boston, Mass.—“Changing Picture of Diabetes.”

Dr. Rufus I. Cole, F.A.C.P., Mount Kisco, N. Y., delivered the Andrew P. Biddle Oration at a public meeting of the Society, September 25.

The Jackson County Health Forum, sponsored by the auxiliaries of all the accredited hospitals of Jackson County, Mo., have announced the following program for 1940-41:

Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill., October 16—“The Nature of Aging and the Chimera of Rejuvenation”;

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., November 20—“What's the Matter with the Patient Who Is Tired All the Time?”;

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., December 18—“The Effects of Narcotics and Alcohol on the Human Body: Facts, Not Opinion”;

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, Okla., February 19—“Glandular Mechanism of the Body”;

Dr. Bernard L. Wyatt, F.A.C.P., Tucson, Ariz., March 19—“Arthritis—the Great Responsibility and Opportunity.”

Dr. Jack C. Norris, F.A.C.P., Atlanta, Ga., spoke on “Technical and Chemical Importance of the Erythrocyte Sedimentation Rates,” and Lieut. Col. James E. Ash, F.A.C.P., (MC), U. S. A., spoke on “Bone Pathology” at the recent annual meeting of the Piedmont Postgraduate Clinical Assembly held at Anderson, S. C. Dr. Edgar A. Hines, F.A.C.P., Seneca, S. C., is President of the Assembly.

The Mississippi Valley Medical Society held its 6th annual meeting in Rock Island, Ill., September 25-27. Among the speakers at this meeting were:

Dr. Walter Lincoln Palmer, F.A.C.P., Chicago, Ill.—“The Diagnosis and Treatment of Gastric Diseases” and “Colitis—Functional and Organic”;

Dr. Leon Unger, F.A.C.P., Chicago, Ill.—“Diagnosis and Treatment of Migraine”;

Dr. Italo F. Volini, F.A.C.P., Chicago, Ill.—“Sulfanilamide and Its Derivatives”;

Dr. David O. N. Lindberg, F.A.C.P., Decatur, Ill.—“Pulmonary Tuberculosis—Practical Points in Diagnosis and Treatment.”

Dr. Unger conducted a private instructional course in “Allergy” and Dr. Volini, “The Treatment of Congestive Heart Failure.”

- Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, "Principles of Hematology," 2nd edition;
- Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., "Simplified Diabetic Management," 3rd edition;
- Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa., "Management of the Cardiac Patient";
- Dr. Samuel A. Levine, F.A.C.P., Boston, Mass., "Clinical Heart Disease," 2nd edition;
- Dr. Robert L. Levy, F.A.C.P., New York, N. Y., "Nomenclature and Criteria for Diagnosis of Diseases of the Heart";
- Dr. Arthur M. Master, F.A.C.P., New York, N. Y., "The Electrocardiogram and X-Ray Configuration of the Heart";
- Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., "Endocrine Therapy in General Practice," 3rd edition;
- Dr. Torald Sollmann, F.A.C.P., Cleveland, Ohio, and Dr. Paul J. Hanzlik, F.A.C.P., San Francisco, Calif., "Fundamentals of Experimental Pharmacology," 2nd edition;
- Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa., "Beyond the Clinical Frontiers";
- Dr. James J. Waring, F.A.C.P., Dr. Abe Ravin (Associate), and Dr. Edward G. Billings (Associate), Denver, Colo., "Directions for Examining Patients."

### *Reprints*

- Dr. J. Edward Berk (Associate), Philadelphia, Pa.—3 reprints;
- Dr. Belford C. Blaine (Associate), Pottsville, Pa.—2 reprints;
- Dr. Leon L. Blum (Associate), Terre Haute, Ind.—1 reprint;
- Dr. Henry O. Colomb, F.A.C.P., Philadelphia, Pa.—1 reprint;
- Dr. Joseph Edeiken (Associate), Philadelphia, Pa.—1 reprint;
- Dr. William Freeman, F.A.C.P., Worcester, Mass.—2 reprints;
- Dr. Thomas N. Hunnicutt, Jr. (Associate), Newport News, Va.—1 reprint;
- Dr. Henry Pleasants, Jr., F.A.C.P., West Chester, Pa.—2 reprints;
- Dr. Henry M. Ray, F.A.C.P., Pittsburgh, Pa.—1 reprint;
- Dr. William S. Reveno, F.A.C.P., Detroit, Mich.—1 reprint;
- Dr. R. Henry Temple (Associate), Kinston, N. C.—1 reprint;
- Dr. Morris M. Weiss, F.A.C.P., Louisville, Ky.—3 reprints;
- Dr. Willard R. Wirth, F.A.C.P., New Orleans, La.—1 reprint;
- Dr. Mast Wolfson, F.A.C.P., Monterey, Calif.—1 reprint;
- Dr. S. E. Wolpaw (Associate), Cleveland, Ohio—2 reprints.

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### SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

The following Boards have announced schedules of their examinations as follows: For further details and application forms communicate with the respective secretaries.

AMERICAN BOARD OF INTERNAL MEDICINE:  
 William S. Middleton, M.D., Secretary  
 1301 University Ave.  
 Madison, Wis.

Written Examination, February 17, 1941.  
 Oral Examination, Boston, April, 1941,  
 in connection with meeting of the  
 American College of Physicians.  
 Oral Examination, Cleveland, June, 1941,  
 in connection with meeting of the  
 American Medical Association.



own life more difficult, he continued to be available at any time of day or night to those who sought his help.

Elsworth Smith's death was mourned by hundreds of St. Louisans who for almost two score years had known him as physician, counselor and friend. To his colleagues it meant not only the loss of a well loved comrade but also the passing of one who perhaps more than any other personified the ethical standards and devotion of the physicians of the last century.

### DR. PERCY MOREAU ASHBURN

Colonel Percy Moreau Ashburn was born July 28, 1872, in Batavia, Ohio, the son of Dr. Allen W. Ashburn. He received his early education in his native city, and graduated from the Jefferson Medical College of Philadelphia in 1893. Three years later Colonel Ashburn married Miss Agnes Davis, the daughter of the late Representative Frank Davis of Ohio. Upon the outbreak of the Spanish-American War he was appointed Contract Surgeon, U. S. A., and within a few months, upon his appointment as First Lieutenant and Assistant Surgeon, he sailed for the Philippine Islands where he took part in the 1899 campaign. During that year he was also executive officer and operating surgeon of the Santa Mesa and First Reserve Hospital in Manila.

Early in 1906 Captain Ashburn had the distinction, with Dr. Charles F. Craig (now Colonel Craig, U. S. A. retired), of organizing the Army Board for the study of tropical diseases in the Philippine Islands. The Board studied filariasis, yaws and dengue, and in that year discovered the method of transmission of the latter by mosquitoes.

In the following year Captain Ashburn was promoted to the rank of Major in the Medical Corps, and two years later he was made a member of the Commission to Liberia for the investigation of medical conditions there. In 1913 he was again detailed as member and president of the Army Board for the study of tropical diseases in the Philippine Islands, and at Ancon, Panama, in the following year became General Inspector of the Health Department in Panama.

In May, 1917, due to the expansion of the Army, Major Ashburn was made a Lieutenant Colonel, and almost immediately was promoted to be a full Colonel. In that year he was detailed as the Chief Medical Officer of the training camp at Fort Benjamin Harrison, going overseas in 1918. While with the American Expeditionary Forces Colonel Ashburn became a member of the commission to examine and report upon the treatment of German war prisoners in Bern. Following the Armistice he was attached to the Department of Sanitation of the Chief Surgeon's office in Tours.

Upon his return to the United States late in 1919, Colonel Ashburn was placed in charge of the Division of Venereal Diseases in the Surgeon General's Office. In 1920 he established the Medical Field Service School in

Medical Association, are:

Dr. Oscar Costa-Mandry, F.A.C.P., San Juan, Chairman  
Dr. Manuel de la Pila Iglesias, F.A.C.P., Ponce  
Dr. César Domínguez (Associate), Humacao

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Dr. George Blumer, F.A.C.P., New Haven, Conn., was the guest of honor at a dinner in June, which was given to mark his retirement from active service at the Yale University School of Medicine. Dr. Blumer joined the staff at Yale as Professor of Theory and Practice of Medicine in 1906. He was the John Slade Ely Professor of Theory and Practice of Medicine from 1908 to 1920, and since 1920 he has been David P. Smith Clinical Professor of Medicine. Dr. Blumer served as Dean of the Medical School from 1910 to 1920.

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Dr. Charles B. Sylvester, F.A.C.P., Portland, Maine, was elected President of the Maine Public Health Association at its 29th annual meeting in Kennebunk, July 11.

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Dr. Robert J. Schneck, F.A.C.P., Detroit, Mich., has been appointed to the Public Welfare Commission of Detroit for a four year term.

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Dr. Nathan B. Van Etten, F.A.C.P., President of the American Medical Association, New York, N. Y., addressed the ninth annual meeting of the Interstate Medical Association held in Chautauqua, N. Y., July 24. Other speakers at this meeting included Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, on "The Care of Anemia," and Dr. Abraham H. Aaron, F.A.C.P., Buffalo, N. Y., on "Self Medication and Its Dangers." Dr. Aaron, Dr. Louis Maxwell Lockie, F.A.C.P., Dr. Clayton W. Greene, F. A. C. P., Dr. Francis D. Leopold, F. A. C. P., and Dr. Frank Meyers (Associate), all of Buffalo, N. Y., conducted a panel discussion on "Recent Advances in Therapeutics."

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At the recent meeting of the Medical Society of Virginia, held jointly with the West Virginia Medical Association at White Sulphur Springs, W. Va., Dr. Henry B. Mulholland, F.A.C.P., Charlottesville, Va., was elected one of the vice presidents.

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Dr. Walter M. Boothby, F.A.C.P., Rochester, Minn., was one of the guest speakers at the 99th annual meeting of the State Medical Society of Wisconsin, which was held in Milwaukee, September 18-20. Dr. Boothby spoke on "Physiologic Problems Involved in Aviation."

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Among the speakers at the annual meeting of the American Association for the Study of Neoplastic Diseases held in Washington, D. C., September 5-7, were:

Dr. Rollin H. Stevens, F.A.C.P., Detroit, Mich.—"Present Day Treatment of Neoplasia" and "What Experimental Biochemistry Suggests for the Future";  
Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C.—"Tumor of the Thyroid Gland";

California School of Medicine from 1913 to 1919, and had been Associate Professor of Diseases of the Chest of the College of Medical Evangelists since 1919. Since 1912, he had been an Attending Physician, tuberculosis division, of the Los Angeles County Hospital. During the World War he was a member of the special board for tuberculosis at Camp Kearney, and at the time of his death was a Captain in the Medical Reserve Corps of the U. S. Army.

Dr. Shulman devoted his interest to diseases of the chest and was instrumental in the founding of the Sanitarium for Tuberculosis at Duarte, of which he was to become Consultant and Chief of Staff. He was a Diplomate of the American Board of Internal Medicine, a member of his county and state medical societies, the American Medical Association, the California State Tuberculosis and the National Tuberculosis Associations, the American Academy of Tuberculosis Physicians, the American College of Chest Physicians, and had been a Fellow of the American College of Physicians since 1923.

Dr. Shulman was an able and earnest worker and was highly respected by his fellow physicians. His active life was closed all too soon. He is survived by his widow, a daughter and a son, Dr. Leon Shulman, Jr.

EGERTON L. CRISPIN, M.D., F.A.C.P.,

Los Angeles, California

### DR. EBEN CLAYTON HILL

Dr. Eben Clayton Hill, F.A.C.P., Baltimore, Maryland, and Temple, New Hampshire, died June 15, 1940, of coronary thrombosis, in the Burbank Hospital, Fitchburg, Massachusetts, at the age of 58 years.

Dr. Hill received his Bachelor of Arts degree in 1903 and his medical degree in 1907 from the Johns Hopkins University. Later he pursued postgraduate training in the Army Medical School and entered the Medical Corps of the Army, serving successively as First Lieutenant (1909-12) and Captain (1913), when he retired for disability in line of duty. Later in his career he was Assistant in Anatomy, Instructor in Anatomy and Associate in Anatomy at the Johns Hopkins Medical School, and served also for many years on the staff of the Vassar Hospital and Dispensary in Poughkeepsie, N. Y. In later years he had been Lecturer in Roentgenology at his Alma Mater.

He was a member of the Medical and Chirurgical Faculty of Maryland, the Baltimore City Medical Society, the American Association of Anatomists, the American Roentgenological Association, a Fellow of the American Medical Association and of the American Association for the Advancement of Science. He had been a Fellow of the American College of Physicians since 1916, and a Life Member since 1938.

Dr. Oscar Costa-Mandry, F.A.C.P., and Dr. Ramón M. Suárez, F.A.C.P., both of San Juan, P. R., have been appointed to the Executive Committee of the Inter-American Institute for Hospital Administrators.

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Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., spoke on "Recent Developments in Gastric Physiology" at the 51st annual meeting of the American Association of Railway Surgeons held in Chicago, September 16-18.

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Dr. Elmer L. Sevringhaus, F.A.C.P., College Governor for Wisconsin, Madison, was one of the speakers at the 45th annual meeting of the American Academy of Ophthalmology and Otolaryngology held in Cleveland, Ohio, October 6-10.

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The Connecticut State Medical Society held its 16th clinical congress in New Haven, Conn., September 17-19. Among the guest speakers were:

Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass.—"Newer Developments in the Treatment of Diabetes";

Dr. Alvan L. Barach, F.A.C.P., New York, N. Y.—"Gas Inhalation Therapy."

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Among the guest speakers at the 151st annual session of the Medical Society of Delaware held in Rehoboth Beach, September 9-11, were:

Dr. John A. Kolmer, F.A.C.P., Philadelphia, Pa.—"The Present Status of Vaccination Against Disease";

Dr. George C. Griffith, F.A.C.P., Philadelphia, Pa.—"The Significance of Precordial Pain";

Dr. Edward Weiss, F.A.C.P., Philadelphia, Pa.—"Renal Aspects of Hypertension";

Dr. Joseph B. Wolfe (Associate), Philadelphia, Pa.—"Atheromatous Cardiovascular Disease."

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Dr. Oscar O. Miller, F.A.C.P., Louisville, Ky., gave the oration in medicine at the annual meeting of the Kentucky State Medical Association held in Lexington, September 16-19. The subject of Dr. Miller's address was "The Evolution of Our Knowledge of Tuberculosis."

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The Michigan State Medical Society held its 75th annual session in Detroit, September 25-27, under the presidency of Dr. Burton R. Corbus, F.A.C.P., Grand Rapids. Among the guest speakers at this meeting were:

Dr. Wallace M. Yater, F.A.C.P., Washington, D. C.—"Surgery of the Heart and the Heart in Surgery";

Dr. Arthur R. Elliott, F.A.C.P., Chicago, Ill.—"Arterial Hypertension: Forty Years in Retrospect";

Dr. Paul A. O'Leary, F.A.C.P., Rochester, Minn.—"Modern Trend in the Treatment of Syphilis";

Dr. John H. Musser, F.A.C.P., New Orleans, La.—"Vitamin and Mineral Requirements in Pregnancy and the Puerperium";

Dr. Thomas T. Mackie, F.A.C.P., New York, N. Y.—"Medical and Surgical Significance of Avitaminosis";

of a distinguished and nationally known authority in the field of tuberculosis, his knowledge of this phase of internal medicine was thorough and deeply rooted.

Dr. Flinn was born in Kingman, Ariz., May 8, 1899, and came to Prescott with his parents in 1902. He received his preliminary education in the Prescott schools. In 1916, at the age of 17, he enlisted with the Canadian Air Force and saw active service in France. He served as an instructor in the Royal Air Force, and in 1918, as results of injuries received in air combat, was invalided home with the rank of first lieutenant. At the beginning of the present war his former chief in the Air Force, now a high ranking officer, offered him a captaincy in the Canadian Medical Corps, which Dr. Flinn declined. After the World War, Dr. Flinn studied medicine in Edinburgh, Vienna and in Halifax. He was graduated from Dalhousie University Faculty of Medicine with the M.D., C.M. degrees in 1932. Before coming to Puerto Rico he practiced medicine in Albuquerque, N. M., and in Prescott, Ariz., and for several years worked at the Pamsetgaaf Sanatorium, Prescott.

His various scientific contributions dealt with blood studies in pulmonary tuberculosis and with pulmonary bronchomoniliasis. During the past six months, and under the auspices of the Department of Health of Puerto Rico, he delivered lectures by radio on different aspects of the tuberculosis problem, and published a paper entitled, "Pulmonary Tuberculosis and Tropical Diseases" in the Puerto Rico Health Bulletin. At the time of his death, Dr. Flinn was an Associate of the American College of Physicians, having joined the College in 1936.

His was a charming and dynamic personality always ready to help his fellowman. By his passing, Puerto Rico loses a leader in the struggle against tuberculosis and his family, friends and associates have suffered an irreparable loss.

R. RODRIGUEZ-MOLINA, M.D., F.A.C.P.,  
San Juan, P. R.

*OBITUARIES*

## DR. ELSWORTH S. SMITH

Dr. Elsworth S. Smith of St. Louis died on June 7, 1940, at the age of 76.

Dr. Smith was born in St. Louis, on January 1, 1864. He was the son of Dr. Elsworth Fayssoux Smith, one of the city's most influential physicians. Through his mother he was a direct descendent of Pierre Laclede, one of the founders of St. Louis. He received his bachelor of arts and master's degrees from St. Louis University and in 1887 graduated from the St. Louis Medical College. He interned at the St. Louis City Hospital, where he was later senior physician and assistant superintendent. In 1900 he entered the private practice of medicine and at about the same time associated himself with the Washington University School of Medicine, where he taught continuously for almost four decades and where for many years he was the Professor of Clinical Medicine. He was a member of the staff of Barnes Hospital from the time of its establishment and for many years previously had visited at the old Washington University Hospital. At one time or another during his life he had served on the staffs of the Mullanphy Hospital, the Barnard Free Skin and Cancer Hospital and the O'Fallon Dispensary.

In 1918 he was president of the St. Louis Medical Society and simultaneously was acting as chairman of the Fourth Medical Advisory Board of the Selective Draft Service and as a member of the Missouri Branch of National Defense. He was one time president of the American Congress of Internal Medicine. His interest and participation in the affairs of the American College of Physicians dated from the day of its founding.

One of the pioneer heart specialists of this country, he was throughout his life a contributor to the literature of circulatory diseases. Although he was nationally well known, it was in St. Louis that his influence was chiefly felt. As the son of a prominent physician and as a member of an old and influential family, he was given at an early age large responsibilities which from the beginning he undertook with modesty but fulfilled with distinction. Always a friend to younger colleagues, he retained throughout his life the intellectual eagerness of youth. Educated in an older school of medicine and living through a period of unprecedented changes in medical practice, he was ever alert to grasp and utilize newer ideas which might serve his patients or add value to his teaching. As a consultant he was superb, and his tempered judgment and sage advice were eagerly sought by his colleagues and by generations of his students. His devotion to his patients was a constant source of inspiration to all who saw him at work. Even during the last years of his life, when personal bereavement and failing health made his

which followed the onset of menstruation was associated with an increased renal excretion of these electrolytes. Studies of the urinary excretion of female sex hormones during the same period indicated a fluctuation in the excretion of female sex hormones which could be correlated in most instances with the cyclical changes in the excretion of sodium, chloride and water. Studies in a control male subject during a period of 40 days revealed only slight fluctuations in the excretion of sodium, chloride and water (3 to 5 day cycle).

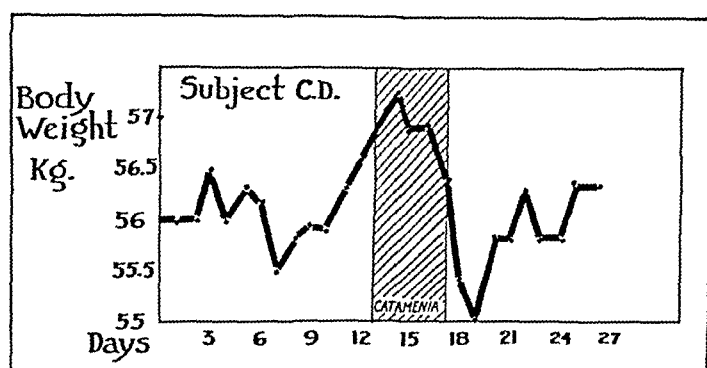


CHART 1. Changes in body weight during the menstrual cycle. Normal subject. Diet uncontrolled.

Patient E. K., a white, married female, 50 years of age, had had a supra-vaginal hysterectomy performed 11 years previously for uterine myomata. The ovaries had been left intact. Electrolyte balance studies\* in this patient revealed a definite cyclical change in mineral excretion during a 24 day period (chart 3). This was associated with a cyclical change in sex hormone excretion. Ovulation and subsequent corpus luteum formation could not be established with certainty in this patient since it was impossible to perform endometrial biopsies. The absence of pregnandiol in the urine of this patient was also consistent with the observations of Venning and Browne on hysterectomized patients.<sup>9</sup>

Patient L. K., a white, married female, 36 years of age, had had a supra-vaginal hysterectomy and bilateral oöphorectomy performed 18 months previously. Electrolyte balance studies\* revealed no significant fluctuation in the urinary excretion of electrolytes during a 30 day period. Furthermore, there appeared to be no significant change in sex hormone excretion during this period. However, the urine did contain a rather high titer of follicle-stimulating hormone. The absence of estrogenic hormone in the

\* These patients were studied on the metabolism ward of The Johns Hopkins Hospital and were permitted to be up and about the ward under supervision. The diet and fluid intake were kept constant. The food was purchased in five day lots and an aliquot, representing one-half of one day's diet, was weighed, dried and analyzed. The diet was so selected that it approximated neutrality. Twenty-four hour urine specimens were collected, measured and preserved with toluene. Electrolyte determinations<sup>6</sup> and assays of estrogenic activity<sup>7</sup> were made on aliquots of three day pooled urine specimens. Pregnandiol was determined according to the method of Venning.<sup>8</sup>

Carlisle, Pennsylvania, becoming its first Director, remaining in Carlisle until 1923 when he was detailed as Professor of Military Hygiene at West Point for a period of four years. In 1927 he was ordered to the Surgeon General's Office to become Chief of the Library Division and Librarian of the Army Medical Library. Colonel Ashburn was retired on account of disability in September, 1931, at the age of 59, but he continued on duty as Librarian until July 1, 1932, when he was relieved from active service. He was appointed Superintendent of Columbia Hospital for Women in Washington, D. C., in 1934, and remained in that position until a few months before his death on August 20, 1940.

He was a member of the American Medical Association and the Association of Military Surgeons, as well as being a Fellow both of the American College of Surgeons and the American College of Physicians.

Colonel Ashburn was recognized as an author of distinction and wrote a number of articles dealing with the work of the Medical Service of the Army. He was also author of two books, one the well-known *Military Hygiene*, and the other the important *History of the United States Army Medical Department*. He was made an officer of the French Legion of Honor in recognition of his distinguished service in the World War.

Colonel Ashburn was a widely known and highly esteemed officer of the Medical Corps. In a varied career in the Army covering more than a third of a century, he was an outstanding figure, and it may be said that he never filled a position without putting something of himself into it. As a student, as a physician, as a scientist, and as a figure in the educational world, he possessed wide culture and progressive knowledge. By nature he was quiet and undemonstrative, and anything approaching self-advertisement was repugnant to him. The writer of this brief tribute knew him well and saw him just as the blow had descended upon him—the knowledge that his death was a matter of but a few weeks. In that interview Percy Ashburn sought no comfort, no palliation of the sentence. He knew the truth and he faced it with singular fortitude and without complaint. He was a faithful servant whose work was well done, and he came to the end with courage and resignation. His friends will not forget him.

HAROLD W. JONES, M.D., Colonel, M.C., U. S. A.,  
The Librarian, Army Medical Library

### DR. LEON SHULMAN

Dr. Leon Shulman, F.A.C.P., Los Angeles, died at his home of coronary disease on September 14. Dr. Shulman was born in Paris, France, on April 7, 1885, but came to the United States as a child, lived and attended high school in Brooklyn, and came to California in 1905.

He received his medical degree from the University of California in 1911. He was a member of the faculty of the University of Southern



urine and the presence of follicle-stimulating hormone were compatible with the diagnosis of primary ovarian deficiency. It is particularly noteworthy that although this patient failed to show any cyclical retention of sodium and chloride at the time of this study, there had been a very definite history of episodes of pre-menstrual edema prior to the removal of the uterus and both ovaries.)

The cyclical retention of significant quantities of sodium, chloride and water in patient E. L., hysterectomized, but with both ovaries intact, suggested that in normal subjects not all of the retention of sodium, chloride and water could be accounted for on the basis of local change in the size of the uterus.<sup>10</sup> Furthermore it appeared that the uterus was neither necessary nor responsible for the phenomenon of cyclical change in renal excretion of electrolytes during the menstrual cycle. The dependence of the phenomenon of cyclical retention of sodium, chloride and water on the presence of functioning ovarian tissue is indicated by the studies on patient L. K. following the removal of the uterus and both ovaries. This is further substantiated by the absence of marked cyclical changes in electrolyte excretion in a normal male control subject. Although these studies suggest that the ovarian hormones have a direct effect on the renal excretion of electrolytes, this fact has not been proved. It is entirely possible that the salt and water retaining-effect of sex hormones may be mediated in part or entirely through other glands of internal secretion.

#### CLINICAL CONSIDERATIONS

1. *Premenstrual "Tension."* Many patients noted puffiness of the eyelids, hands, feet or abdomen during the 48 hours immediately preceding the onset of menstruation. These signs were usually accompanied by headache and some degree of abdominal distention. In most instances symptoms were not severe and did not require treatment.

2. *Generalized Premenstrual Edema.* Fortunately the incidence of patients presenting signs and symptoms of generalized fluid retention during the premenstrual period was small. Great benefit was obtained by weight reduction when the patient's weight exceeded normal,\*<sup>11</sup> by absolute restriction of sodium chloride in the diet during a 7 to 10 day period preceding the onset of menstruation and by the administration of supplementary potassium therapy. Potassium therapy greatly augmented the effectiveness of the low-sodium diet. Potassium citrate, 10 c.c. of a 20 per cent solution, was given in fruit juice, two or three times daily (total of 30 c.c. daily).

3. *Unexplained Gain in Weight During Treatment for Obesity.* Frequently during the course of treatment for obesity by means of a low caloric diet, female patients, much to their discouragement, either failed to lose weight or actually gained. A sudden gain in weight during the course of dietary restriction was not only discouraging to the patient but was also

\* The method of Willoughby<sup>11</sup> for estimating ideal weight is recommended.

## DR. WILLIAM COLE

Dr. William Cole, F.A.C.P., Long Beach, California, died July 9, 1940, of coronary sclerosis, at the age of 48. He was born at Melita, Man., Canada, April 13, 1892. He graduated from the University of Manitoba Faculty of Medicine in 1913, and served during the World War in the Royal Canadian Army Medical Corps with the rank of Captain, with service in Canada, England, Belgium and France. He was a member of the Visiting Staff of the Long Beach Community, St. Mary's Long Beach and Seaside Memorial Hospitals.

Dr. Cole was a registrant of the General Medical Council of Great Britain, Diplomate of the American Board of Internal Medicine and a member of the Long Beach Academy of Medicine, Los Angeles County Medical Association, California Medical Association, American Medical Association, American Association for Study of Rheumatism, and had been a Fellow of the American College of Physicians since 1932.

## DR. WILLIAM ALBERT EVANS

Dr. William Albert Evans, F.A.C.P., Detroit, Michigan, died June 9, 1940, of coronary occlusion, at the age of 63. He was born in Ontario, Canada, in 1876, and received his medical degree from the University of Michigan in 1902. He had served as Roentgenologist at the Harper, U. S. Marine and Manufacturers' Hospitals, and at one time was Associate Professor of Roentgenology at Wayne University College of Medicine. For several years he was President of the Detroit Board of Health.

Dr. Evans was a member of the Wayne County Medical Society, Michigan State Medical Society, Radiological Society of North America, the American College of Radiology, and a member of the Executive Council and a past President of the American Roentgen Ray Society. He was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1917.

## DR. ZEBUD MacKAY FLINN

Dr. Zebud MacKay Flinn (Associate), Bayamon, P. R., passed away after a brief illness on August 3, 1940, at the Presbyterian Hospital in San Juan, P. R., at the untimely age of 41. In October, 1939, he arrived in Puerto Rico, working as resident physician at San Alberto Hospital in Bayamon until June, 1940, when he was asked to join the active campaign against tuberculosis conducted by the Health Department of the Island, being assigned for duty at the Ponce Hospital. Dr. Flinn arrived in Puerto Rico with an unusual background in the field of tuberculosis. He was the son of Dr. and Mrs. John W. Flinn, F.A.C.P., of Prescott, Ariz. Scion

and chloride in the diet, supplemented by added potassium therapy (vide supra) aided greatly in reducing the retention of salt and water. Sufficient fluid was permitted to ensure a 24-hour urine volume of 1500 c.c. This form of therapy, however, was limited to a 4 to 7 day period preceding menstruation. With the onset of menstruation, all therapy with the exception of the low caloric diet, was discontinued immediately.

4. *Nephritis, Hepatic Cirrhosis with Ascites, Hypoproteinemia and Local Obstruction to Venous or Lymphatic Flow.* Female patients suffering from disorders which predispose to water retention may accumulate excessive quantities of extracellular fluid during the premenstrual period. The rapid appearance of edema in these patients at this time often suggests an exacerbation of the underlying disease.

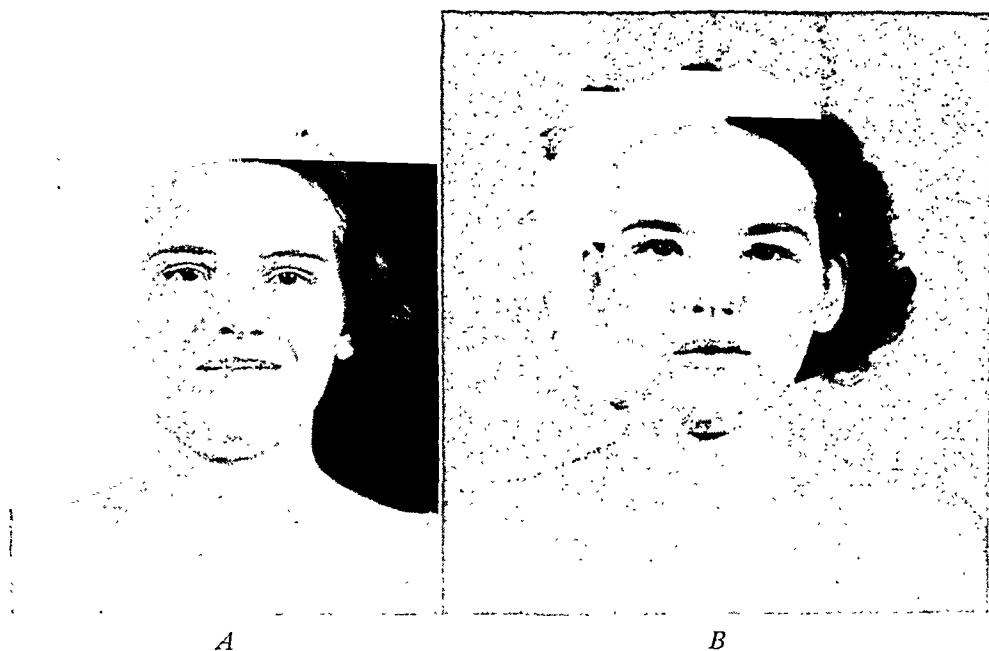


FIG. 1. *A* was taken on the ninth day of the study. *B* was taken on the fourteenth day of the study. (See chart 5.)

Patient D. W., a white, married female, 26 years of age, suffering from chronic glomerular nephritis, had noted that on several occasions a sudden, marked transient edema had appeared 24 to 48 hours preceding the onset of menstruation (figure 1). The appearance of edema was associated with a reduced urinary output and a striking gain in weight. Shortly after the onset of menstruation an increase in urine volume was noted, the edema rapidly disappeared and there was marked weight loss (chart 5). The rapid, spontaneous disappearance of the edema with the onset of menstruation made it appear unlikely that an exacerbation of the nephritis had occurred. Furthermore, no change was observed in the quantity of albumin or formed elements in the urine at that time.

# ANNALS OF INTERNAL MEDICINE

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## THE RÔLE OF GONADAL AND ADRENAL CORTICAL HORMONES IN THE PRODUCTION OF EDEMA\*†

By GEORGE W. THORN, F.A.C.P., *Baltimore, Maryland*, and KENDALL  
EMERSON, JR., *New York, N. Y.*

### FEMALE SEX HORMONES

THE occurrence of generalized edema, associated with menstruation has been reported by Thomas,<sup>1</sup> Sweeney,<sup>2</sup> Molnar and Gruber<sup>3</sup> and Atkinson and Ivy.<sup>4</sup> Experimentally it has been observed<sup>5</sup> that the intramuscular injection of large doses of crystalline sex hormones (estrone, estradiol, testosterone and progesterone) in both male and female dogs resulted in a striking, but temporary, retention of sodium, chloride and water. Qualitative as well as quantitative differences were also noted in the effect of treatment with sex hormones on the renal excretion of potassium, phosphate and nitrogen.<sup>5</sup>

In a recent study<sup>6</sup> it was noted that 24 of a group of 50 normal female subjects gained 1 kg. or more during the week immediately preceding menstruation. Shortly after the onset of menstruation (24 to 72 hours) a diuresis occurred and the subjects lost weight. Less frequently a transient gain in weight was noted at, or about, the expected time of ovulation. In a limited number of subjects it was possible to establish the approximate date of ovulation by determining the time at which pregnandiol, an excretion product of progesterone (corpus luteum), appeared in the urine.

In subjects in whom there was no dietary restriction (chart 1) it is possible that an increased ingestion of food was responsible in part for the total weight gain which occurred premenstrually.<sup>6</sup> However, carefully controlled balance studies in other subjects (chart 2) revealed that under constant dietary conditions, the premenstrual gain in weight was associated with a striking retention of sodium, chloride and water. The diuresis

\* Read at the Cleveland Meeting of the American College of Physicians, April 3, 1940.  
From the Chemical Division, Medical Clinic, The Johns Hopkins University and Hospital, Baltimore, Maryland.

† Aided, in part, by a grant from the Committee on Research in Endocrinology, National Research Council.

studies in dogs<sup>5</sup> indicated that although testosterone treatment was associated with a striking retention of nitrogen, phosphorus and potassium, appreciable quantities of sodium, chloride and water were also retained, particularly during the initial period of treatment. Similar observations were made on a male subject following testosterone propionate therapy (chart 6). In this patient, treatment was followed by a striking retention of sodium, chloride and water, associated with a rapid gain in weight. Withdrawal of treatment was followed within 48 hours by an increase in the renal excretion of sodium, chloride and water with a corresponding loss in body weight. The recent studies of Kenyon, et al.<sup>12</sup> indicate that a large part of the initial weight gain in eunuchs treated with testosterone can be accounted for on the basis of sodium, chloride and water retention. Since testosterone propionate is not strikingly potent in its "sodium-retaining effect"<sup>5</sup> excessive salt and water retention is not a frequent complication of clinical treatment with this hormone.

#### ADRENAL CORTICAL HORMONES

Recent studies indicate a close chemical relationship between the sex hormones, particularly progesterone, and certain adrenal cortical hormones, particularly desoxycorticosterone.<sup>13</sup> As might be anticipated, there is some overlapping in the physiological action of the two groups of compounds.

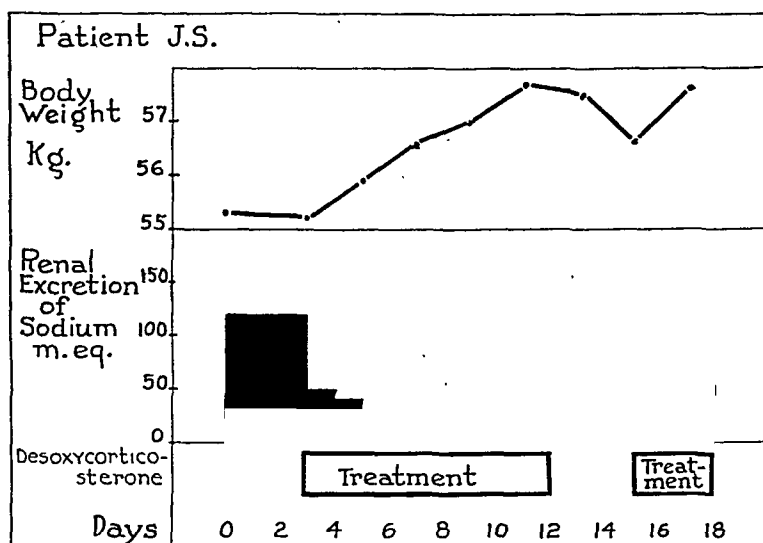


CHART 7. Effect of desoxycorticosterone acetate treatment on body weight and renal excretion of sodium. Addison's disease. Constant diet. (The daily intake of sodium was 80.4 m. eq.)

Thus it has been observed that treatment with progesterone greatly increased the period of survival of bilaterally adrenalectomized animals.<sup>14</sup> Furthermore the similarity in the clinical picture produced by certain tumors of the adrenal cortex and by arrhenoblastomata of the ovary is well known.

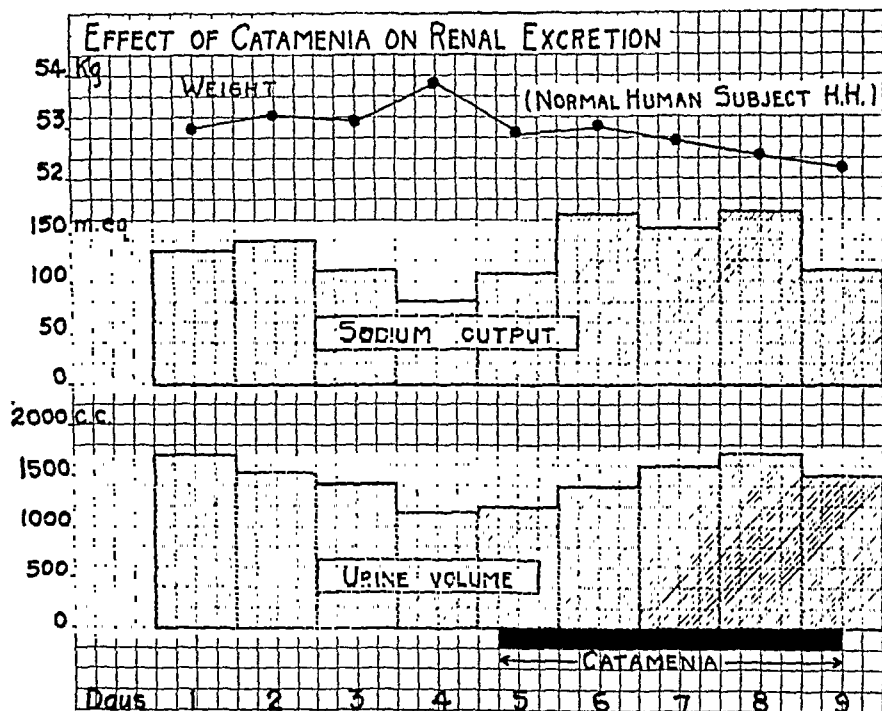


CHART 2. Premenstrual retention of sodium and water. Normal subject. Constant diet and fluid intake. (The daily intake of sodium was 122.4 m. eq.)

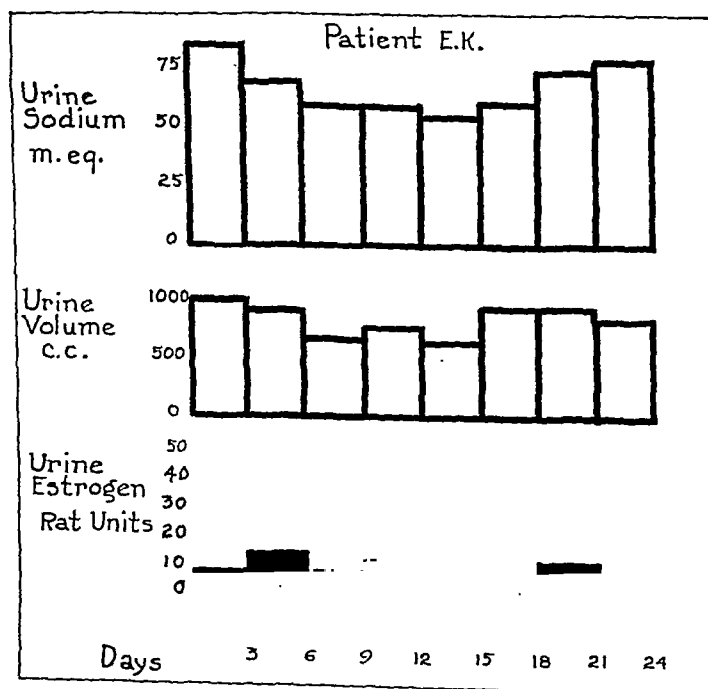


CHART 3. Cyclical change in urinary excretion of sodium, water and estrogen. Hysterectomized patient. Constant diet and fluid intake. (The daily intake of sodium was 78.0 m. eq.)

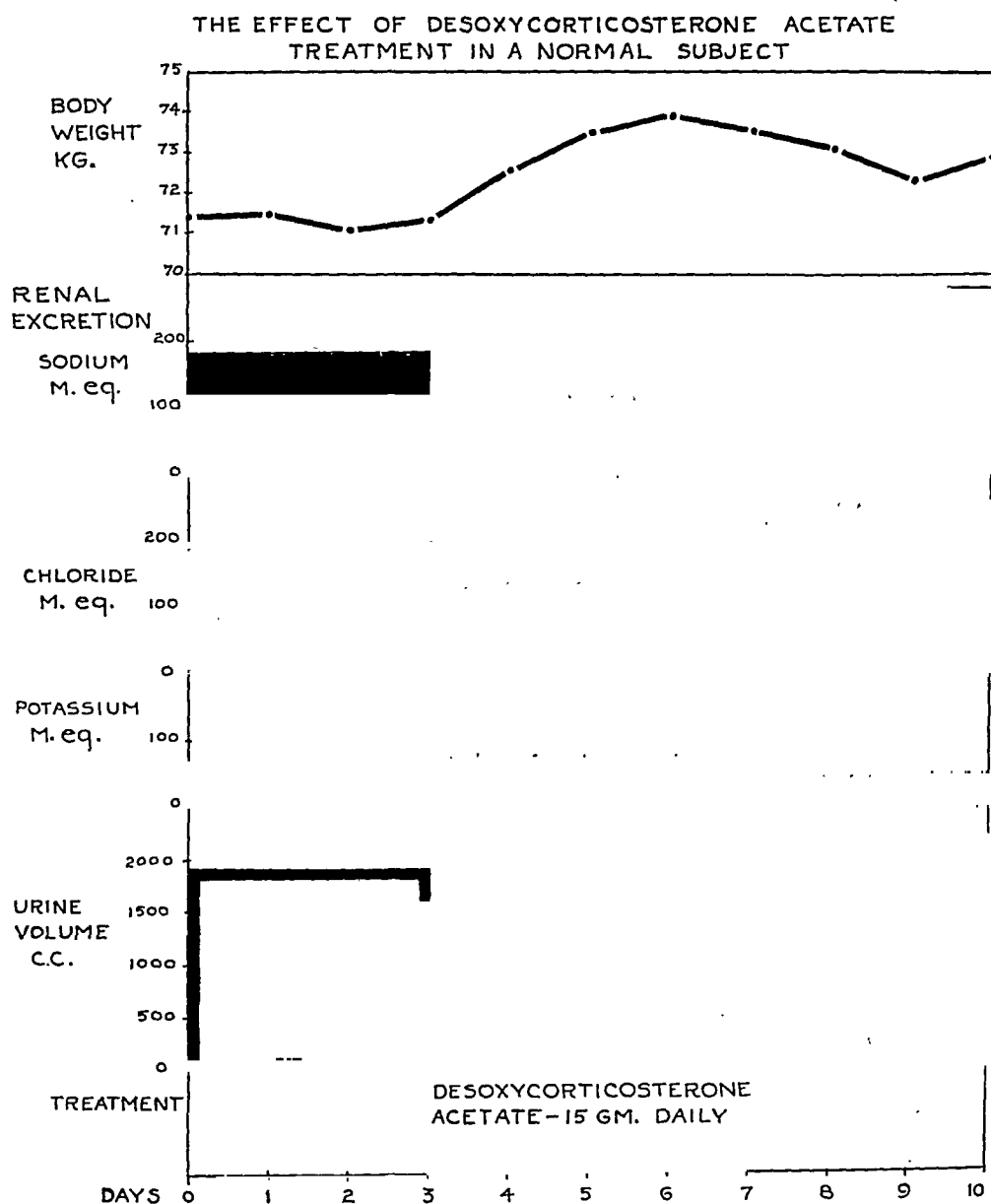


CHART 8. The effect of desoxycorticosterone acetate treatment on body weight and renal excretion of electrolytes (normal subject). The constant diet contained 192.1 m. eq. of sodium, 203.5 m. eq. of chloride and 84.0 m. eq. of potassium.

of the adrenal cortex which were the antithesis of those observed in patients with Addison's disease.

### DISCUSSION

It cannot be stated from clinical studies which of the female sex hormones plays the more important rôle in regulating electrolyte balance. Certainly, the retention of electrolytes during the premenstrual period is much more striking than that which is observed at the time of ovulation. This

perplexing to her physician whose first reaction was to suspect dietary indiscretions.

In several patients it was observed that the gain in weight during a dietary regimen of low caloric intake was related to a temporary retention

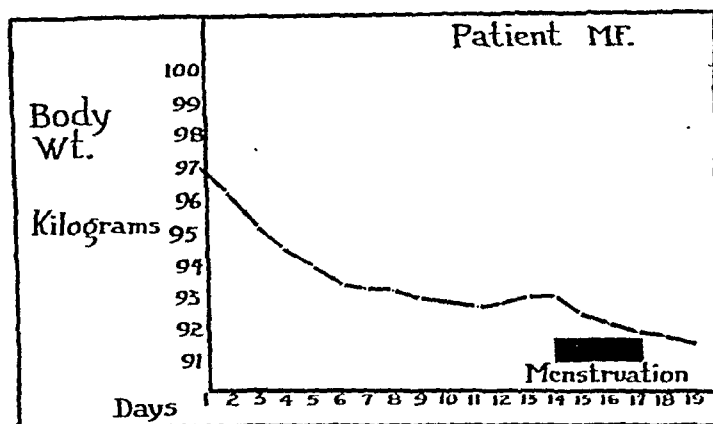


CHART 4. Premenstrual gain in weight during constant, low-calorie dietary regimen for treatment of obesity.

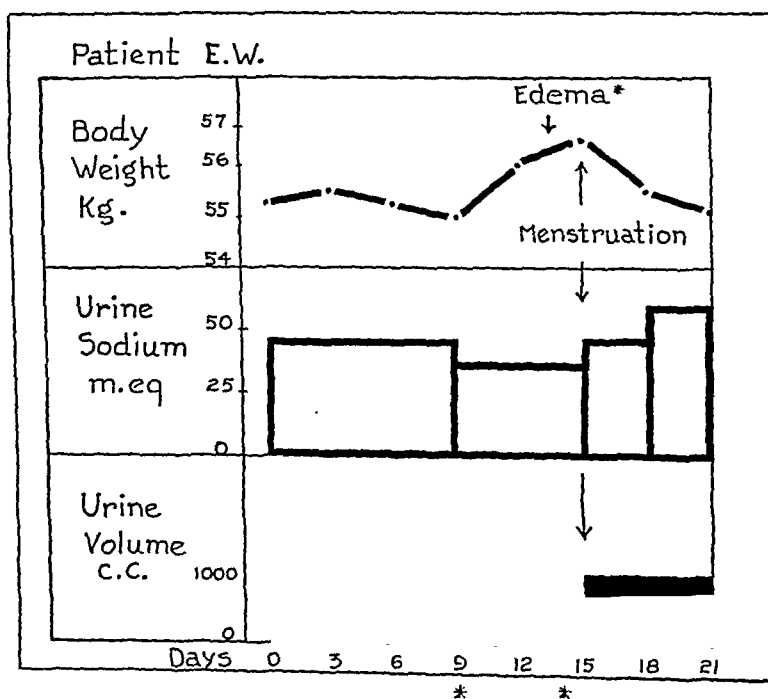


CHART 5. Premenstrual edema in patient with nephritis (constant diet). The daily intake of sodium was 44.4 m. eq.

of sodium, chloride and water during the premenstrual period (chart 4). Following the onset of menstruation a diuresis usually occurred and the patient lost weight. The ability to predict these episodes was of great aid in the care and treatment of obese female patients. Restriction of sodium



patients with some underlying change which predisposes to excessive retention of sodium, chloride and water.

### SUMMARY

In normal women cyclical changes in female sex hormone excretion were observed to be associated with striking changes in the excretion of sodium, chloride and water. Similar changes were also observed in a patient who had been hysterectomized several years previously. In a patient who had had both ovaries and uterus removed 18 months previous to this study no cyclical change in sex hormone excretion or electrolyte balance was noted during a period of 30 days.

In obese patients a transient gain in weight was occasionally observed during a weight-reducing regimen. In some instances, the gain in weight could be accounted for by a premenstrual retention of sodium, chloride and water. A retention of sodium, chloride and water also occurred during the premenstrual period of patients suffering from disorders which predisposed to fluid accumulation such as nephritis, cirrhosis of the liver with ascites, hypoproteinemia, and obstruction to venous or lymphatic circulation. Unless fully appreciated, the premenstrual retention of fluid in these patients could be mistaken for an exacerbation of the underlying disease.

Although retention of an appreciable quantity of sodium, chloride and water occurred during the initial period of testosterone propionate therapy, edema was neither a frequent nor striking complication of male sex hormone therapy.

Desoxycorticosterone acetate therapy has a very striking sodium, chloride and water-retaining effect in normal subjects as well as in patients with Addison's disease. Great care must be exercised in the use of this hormone clinically, if excessive retention of these electrolytes is to be avoided.

Sodium chloride restriction and supplementary potassium medication were effective in moderating the sodium, chloride and water-retaining effect of both gonadal and adrenal cortical hormones.

### CONCLUSIONS

The electrolyte balance of the body appears to be affected significantly by the steroid hormones of the gonads and adrenal cortex. Under certain conditions, these hormones may act as precipitating factors in the production of edema. Careful restriction of sodium chloride intake combined with supplementary potassium medication provides effective therapy in preventing or ameliorating the edema. Such therapy should not be used indiscriminantly.

The authors are indebted to Miss Mildred Caldwell, Supervisor of the Metabolism Ward, Miss Elizabeth Olsen, Dietician-in-Charge of the Metabolism Ward, Mr. Howard F. Conn and Drs. Daniel Kuhlmann and R. Palmer Howard for their continued assistance and coöperation.

The volume of ascitic fluid in patients with hepatic cirrhosis was observed to increase during the premenstrual period. With the onset of menstruation an appreciable reduction in ascites was noted. This was associated with a diuresis and loss in weight. Patients with a low concentration of serum protein and patients with obstruction to venous or lymphatic circulation were also observed to retain excessive quantities of sodium, chloride and water during the premenstrual period. Frequently the excessive retention of fluid at this time resulted in the appearance of edema. Following the onset of menstruation the edema disappeared rapidly.

In the treatment of edema in patients with nephritis, it is desirable to use a diet of alkaline ash in addition to a restricted sodium chloride intake. Added potassium therapy is contraindicated in these patients, as an increase in serum potassium frequently complicates the renal disease. In patients with edema, without demonstrable renal damage, the premenstrual retention of fluid may be greatly reduced by restricting the sodium chloride intake and by administering supplementary potassium medication during this period.

#### MALE SEX HORMONES

The striking and immediate gain in weight which follows testosterone propionate therapy in castrate male patients is well known. Experimental

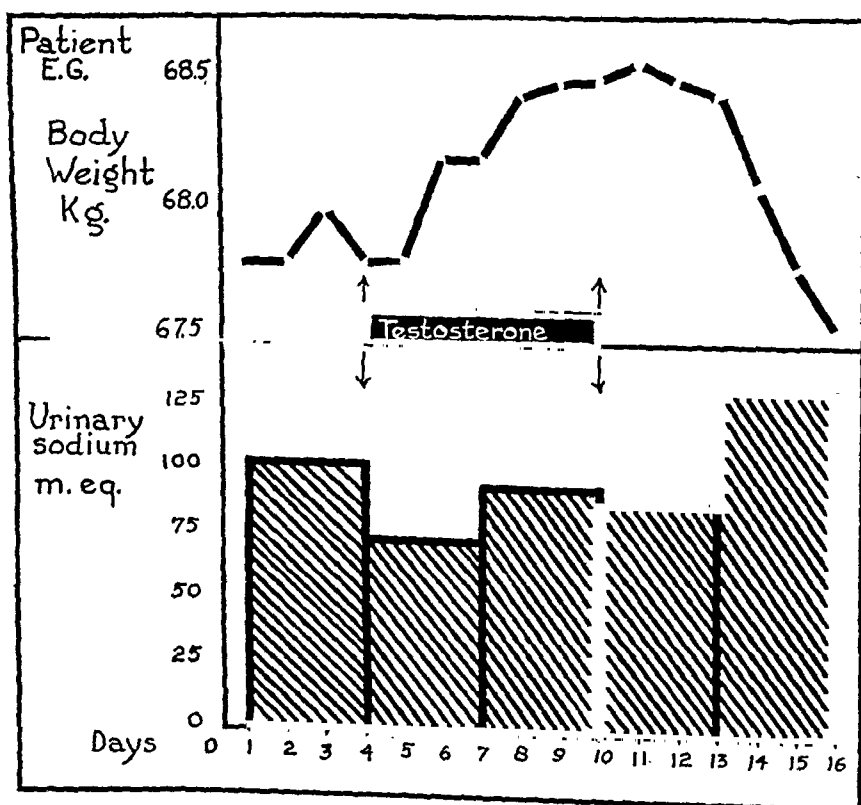


CHART 6. Retention of sodium during testosterone therapy. Constant diet. The daily intake of sodium was 100.0 m. eq.

# DILANTIN SODIUM: ITS INFLUENCE ON CONDUCT AND ON PSYCHOMETRIC RATINGS OF INSTITUTIONALIZED EPILEPTICS \*

By ALEXANDER T. ROSS, M.D., *Indianapolis, Indiana*, and VIRGINIA JACKSON, A.B., *Caro, Michigan*

REPORTS on the effectiveness of sodium diphenyl hydantoinate (dilantin sodium) in epilepsy have accumulated rapidly since Merritt and Putnam<sup>1</sup> inaugurated the use of the drug in 1938. Naturally most interest has devolved upon its use in the control of convulsions and upon its toxic effects—rash, anorexia, nausea, vomiting, ataxia, gingivitis,<sup>2</sup> and to a less extent delusions, hallucinations, prolonged confusion, agitation, depression, irritability, and suspiciousness.<sup>3, 4</sup> The toxic effects apparently are manifested earlier, more frequently, and more severely in patients over 40 years of age, and consequently the drug would seem to be of less danger in younger and better preserved individuals.<sup>5</sup>

In consonance with the alleviation of seizures almost all reports on dilantin sodium remark on the improvement in behavior, well-being, cooperation, alertness, general attitude, irritability, temperament, and personality of many patients.<sup>3, 4, 6, 7, 8, 9</sup>

We have been particularly interested in the effects of the drug on conduct, as well as on any change that might be reflected in intelligence and performance tests. For this study we have used 73 patients at the Caro State Hospital for Epileptics who have received dilantin sodium over a period of 12 to 18 months. The dosage ranged from 0.1 gm. (gr. 1½) to 0.5 gm. (gr. 7½) daily, depending upon anticonvulsant effects. The vast majority of patients were between 17 and 30 years of age, the youngest being 11 and the oldest 51 years. By "conduct" we included behavior, irritability, alertness, initiative, interest, general attitude, and coöperation, taking the sum total of these factors as determining the effect of the drug. The 1937 Revised Stanford-Binet was used for the determination of the intelligence quotient, and Grace Arthur's Point Scale of Performance Test for the performance quotient. On 55 of the subjects the intelligence quotient was compared with that obtained prior to the use of dilantin sodium, and on 25 the performance quotient was so compared.

Using the classification of the epilepsies adopted by the National Association for the Study of Epilepsy, we divided the patients into the following groups: 29 with idiopathic epilepsy; 25 whose epilepsy is a manifestation of cerebral agenesis; 12 whose convulsions reflect a previous meningo-encephalitis; and 7 whose epilepsy is ascribed to cerebral trauma.

Our results are summarized in the accompanying table.

\* Received for publication May 6, 1940.

From the Caro State Hospital for Epileptics, R. L. Dixon, M.D., Superintendent.

The rôle which the adrenal cortex plays in the regulation of electrolyte balance is of great importance.<sup>15</sup> It has been demonstrated that treatment with adrenal cortical extract resulted in a striking retention of sodium, chloride and water in patients with Addison's disease as well as in normal subjects.<sup>16</sup> In the past, however, edema has been an infrequent complication of adrenal extract therapy since the costliness of extract necessarily limited the quantity of hormone which could be administered. The synthesis of desoxycorticosterone acetate, however, has made available a very potent adrenal cortical hormone preparation at a cost which most patients can afford.

Treatment with desoxycorticosterone acetate resulted in a striking retention of sodium, chloride and water in patients with Addison's disease (chart 7).<sup>17, 18</sup> Treatment with synthetic hormone was associated on occasions with the retention of excessive quantities of salt and water with the appearance of edema.<sup>18</sup> This complication occurred most frequently when supplementary sodium chloride therapy was given. Great care must be exercised in the administration of desoxycorticosterone acetate therapy if excessive salt and water retention is to be avoided. Restriction of sodium chloride intake and supplementary potassium medication (*vide supra*) are effective measures in preventing or reducing edema resulting from desoxycorticosterone acetate therapy.

A striking retention of sodium and chloride was observed in a group of five normal subjects during treatment with daily intramuscular injections of 10 to 15 mg. of Percorten \* (Ciba, desoxycorticosterone acetate in sesame oil) (table 1 and chart 8). The subjects were maintained on a constant diet supplemented with 9 gm. of added sodium chloride. During a period of four days of treatment an average weight gain of approximately 1.5 kg. was observed. The retention of sodium and chloride during this period was accompanied by an increased excretion of potassium. Blood studies revealed a slight increase in the serum concentration of sodium and chloride despite hemodilution. No significant change in blood pressure was observed during the short period of hormone therapy. Slight puffiness of the face and ankles was observed in two of the normal subjects on the fourth day of treatment. Withdrawal of hormone therapy was followed by a marked excretion of sodium, chloride and water, weight loss, retention of potassium; hemoconcentration, a decrease in the serum concentration of sodium and chloride and a significant increase in serum potassium.

The increased sodium, chloride and water retention which occurred in normal subjects during the period of treatment with desoxycorticosterone acetate is of interest in relation to the studies of Anderson et al.<sup>19</sup> These investigators have reported electrolyte changes in patients with hyperfunction

\* The Percorten, desoxycorticosterone acetate in sesame oil, used in this study was provided through the courtesy of Dr. E. Oppenheimer, Ciba Pharmaceutical Products, Inc., Summit, N. J.

particular field—in some patients greatest improvement was shown in memory, in others reasoning and planning, in still others recognition of verbal absurdities.

On the Grace Arthur Performance Scale nine patients raised their quotients over 10 points, three of them from 30 to 44 points, while three reduced theirs. Eleven of the 12 had experienced a marked reduction in seizures; the twelfth had only a slight drop but scored a rise of 44 points in performance quotient. The improvement was mainly manifested by quicker perception, better planning, and speedier execution of the tests.

### DISCUSSION

In evaluating the effects of any medicinal agent in the treatment of institutionalized epileptics, certain intangible factors must be considered. Suggestion plays a rôle, but we believe we have extended the trial period long enough (12 to 18 months) to eliminate this factor. Environment must be taken into consideration, for most epileptics living in overcrowded institutional quarters and with the average mentality of such intramural patients, are irritable, explosive, and easily disquieted under certain circumstances. One or two uncoöperative, aggressive individuals can upset an entire group. Perhaps more of our patients would have shown improvement in conduct had they been in an environment free of overcrowding, tension, restlessness, and distraction. Nevertheless, they had all been in the institution long enough to have become adjusted to their surroundings and the attendant disturbances. We believe, therefore, that in this study too great weight need not be placed upon the effect of environment. Another possibility is that the improvement was spontaneous since we know that sometimes for no apparent reason some epileptics will gradually have fewer and fewer seizures and maintain a stationary level of deportment and intellectual activity. Our study group is too large to suggest that most of the improvement could be so explained.

Undoubtedly much of the betterment in conduct was due to the pronounced reduction in the number of seizures, giving these patients a greater feeling of security, lessening the hazards of attacks, and producing a sense of well-being and possibly elation. While this may be so, there were just about as many instances where a similar reduction of attacks was obtained in essentially the same types of individuals without producing an appreciable change in conduct. We have no explanation for this discrepancy.

One might expect that with the heightening of interest, initiative, and alertness shown by many of the patients, their intelligence ratings would be raised. They actually give the impression of being more intelligent than at the beginning of treatment. However, this appearance is deceptive for there obtained practically a balance between raised and lowered intelligence ratings in the face of equivalent seizure reduction. These results agree essentially with those reported by Fetterman<sup>4</sup> who found that dilantin showed no un-

TABLE I

The Effect of Desoxycorticosterone Acetate Treatment on the Renal Excretion and Serum Concentration of Electrolytes in Normal Subjects

Average daily value for 5 normal subjects	March 17-20 Control	March 20-24 Treatment	March 24-27 Control
Urinary Studies			
Urine volume c.c.	1468	1200	1591
Urinary sodium m.eq.	175.2	94.0	244.8
Urinary chloride m.eq.	184.6	122.6	240.4
Urinary potassium m.eq.	65.8	80.5	43.3
Urinary inorganic phosphorus gm.	.834	.875	.880
Urinary ammonia nitrogen gm.	.533	.641	.636
Blood Studies			
Serum sodium m.eq. per liter	139.1	141.9	139.4
Serum chloride m.eq. per liter	100.5	106.1	95.8
Serum potassium m.eq. per liter	4.9	5.2	6.3
Serum carbon dioxide combining power m.eq. per liter	28.5	29.3	28.5
Blood non-protein nitrogen mg. per 100 c.c.	35	33	34
Blood sugar mg. per 100 c.c.	93	88	91
Total serum protein gm. per 100 c.c.	7.11	6.61	6.64
Hematocrit: per cent volume of packed cells	46.2	43.3	46.2

suggests the possibility that progesterone, or progesterone in addition to estrogens, is more effective than the estrogens alone. In experimental studies<sup>5</sup> it has been demonstrated that the effect of progesterone on electrolyte balance resembles more closely the effect of adrenal cortical hormone than either estrone or testosterone. Furthermore, the increased survival period of adrenalectomized animals treated with progesterone,<sup>14</sup> suggests that progesterone has a significant sodium and chloride-retaining effect, since prolongation of the survival period of these animals parallels closely the ability to maintain electrolyte balance.

It appears unlikely that an increase-over-normal in the secretion of sex hormones is the factor responsible for the premenstrual edema noted in these patients. The absence of edema in most normal patients, and the greatly increased retention of electrolytes which was observed in patients suffering from complications which favored the accumulation of excessive quantities of fluid, suggest that premenstrual edema is probably the result of normal cyclical changes in sex hormone secretion acting as a precipitating factor in

# THE BLOOD SEDIMENTATION TEST AS A ROUTINE DIAGNOSTIC PROCEDURE; A CLINICAL EVALUATION OF 2063 CASES \*

By E. B. AGNOR, M.D., *Atlanta, Georgia*

THE blood sedimentation test, one of the oldest and simplest of the laboratory procedures, was reestablished as a test for pregnancy by Fåhræus<sup>1</sup> in 1918. Although the specificity of the test for pregnancy was soon disproved, the procedure has received much attention since that time. In this country it has been used most frequently as a special rather than as a routine procedure.

The larger portion of the literature dealing with the sedimentation test has been concerned with the factors influencing the rate, the various methods of determination, and the results obtained from the use of the test in certain diseases. Few authors have recorded observations based upon the routine use of the test. Cutler<sup>2</sup> reported his experience with the sedimentation test based upon the study of 5,000 cases observed in hospital, dispensary, and office practice. Schattenberg<sup>3</sup> used the sedimentation test as a routine procedure in 1,100 cases consisting of applicants for health cards in the Dallas City Health Department, and patients in the outpatient dispensary of Baylor University. Gallagher<sup>4</sup> performed the test routinely in 685 cases as a part of the yearly health examination of preparatory school students. Wintrobe<sup>5</sup> used the test as a routine procedure in 767 cases in the diagnostic clinic of the Johns Hopkins Hospital. These authors agreed that the routine blood sedimentation test was of value. Other authors have stressed the value of the sedimentation test as a routine procedure, but without supporting evidence.

## MATERIAL AND METHODS

*Material.* The present study is based upon a survey of the records of 2,063 patients observed in the Diagnostic Hospital of the New England Medical Center. The blood sedimentation test was performed as a routine procedure. The purpose of this study is an evaluation of the test in these cases. The patients were all hospital cases and represented all types of disease. As shown in table 1, the group was composed largely of adults, and only cases which had been completely studied were included.

*Methods.* The blood sedimentation tests were performed by a modification of the Westergren method,<sup>6</sup> which differed from the original only in that 5 per cent sodium citrate solution was used as the anticoagulant. Throughout the study the rate for a given patient was the routine admission

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From the Joseph H. Pratt Diagnostic Hospital.

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*Group IV.* Definitely Elevated Sedimentation Rate—rates greater than 30 millimeters at the end of one hour.

Table 2 shows the distribution of the sedimentation rates.

TABLE II  
Distribution of the Sedimentation Rates

Sex	Sedimentation—mm. per hr.				Total Cases	Total Elevated Rates
	0-15	16-20	21-30	31 +		
Male.....	560 56.6%	76 7.6%	99 10%	255 25.8%	990	354 35.8%
Female.....	611 57.0%	114 10.6%	124 11.5%	224 20.9%	1073	348 32.4%
Totals.....	1171 56.7%	190 9.2%	223 10.8%	479 23.3%	2063	702 34.1%

### DISCUSSION OF RESULTS

*Results.* Blood counts, urinalyses, and serological tests for syphilis are widely employed as routine diagnostic procedures. The purpose of this study is to indicate that the blood sedimentation test is important enough to be similarly employed even though it is non-specific.

In this series there were 176 cases, 8.5 per cent, showing changes in the serologic reactions of the blood, Wassermann, Hinton and Kahn tests having been performed. Similarly, there were 331 cases, 16 per cent, showing an abnormal blood count which gave specific information leading to the detection of the particular disease. Also, 207 cases, 10 per cent, were found to have some disease in which the urinalysis had given specific information leading to a diagnosis. Therefore, in 34.5 per cent of our cases the generally employed routine diagnostic tests were of specific value. On the other hand, a total of 702 cases, 34.1 per cent, showed an increased sedimentation rate, which, though not specifically, yet definitely indicated the presence of disease. However, these cases must be further analyzed to determine more accurately the value of the information obtained by the use of the sedimentation test as a routine diagnostic procedure.

*Relationship of the Sedimentation Rate to the Diagnosis.* The cases were divided into a group presenting no evidence of an organic disease, which may be considered as "negative"; and a group showing definite evidence of disease, which may be considered as "positive." This division was based upon the discharge diagnosis as recorded on the case record, grouped according to the "Standard Classified Nomenclature of Disease."<sup>9</sup> There was no doubt in the minds of the observers as to the absence of evidence of organic disease in the "negative" group. Insignificant organic disease,

TABLE I

	Idio- pathic	Agen- esis	Enceph- alitis	Trauma
Number of patients	29	25	12	7
Monthly seizure average of group before medication	510	666	398	215
Monthly seizure average of group during medication	87	153	154	42
Seizures decreased 75% or more	20	15	5	6
Seizures decreased 50%-75%	5	4	5	0
Seizures decreased 25%-50%	2	5	0	0
Seizures unimproved or increased	2	1	2	1
Conduct improved	14	9	3	3
Conduct unchanged	14	15	7	4
Conduct worsened	1	1	2	0
Rechecks 1937 Revised Binet	26	17	7	5
I.Q. raised over 10 points	6	1	1	0
I.Q. decreased over 10 points	4	0	1	0
Rechecks Grace Arthur	13	5	4	3
P.Q. raised over 10 points	4	1	3	1
P.Q. decreased over 10 points	1	2	0	0

The most striking feature is that in over 65 per cent of the patients the seizure incidence was reduced 75 per cent or more. The least reduction occurred in the encephalitic group, whereas the greatest was in the small traumatic group.

In a little less than one-half of the patients there was improvement in conduct. Here again the encephalitic group was less responsive than the others. One patient with idiopathic epilepsy, whose seizures were almost totally controlled, exhibited remarkable improvement in behavior, interest, and coöperation. Dilantin was withdrawn and, though he has had no recurrence of convulsions, he has returned to his former vituperative, surly, resistive manner. In another idiopathic epileptic, whose convulsions were quite well controlled by the drug, there was a repetitious occurrence of disturbed periods marked by paranoid ideas, auditory hallucinations, assaultiveness, and general battering-ram tactics. When dilantin was discontinued he again became the rather ingratiating, docile person he had been before the drug was administered, despite a sharp increase in the number of convulsions. In three patients the conduct change consisted of increased irritability, querulousness, and suspiciousness. Seizures had been considerably reduced in two of these boys, and increased a few in the other.

The comparison of psychometric results before and after dilantin administration was interesting. Although in comparing test results a variation of over 5 points is considered significant, we have selected a range of 10 points as being more indicative of a worthwhile variation between the former and latter determinations. The intelligence quotient was raised over 10 points in six idiopathic epileptics and reduced over 10 points in four others. All but one of these 10 individuals had a pronounced diminution in seizure incidence. One each of the agenesis group and of the encephalitic group likewise raised their intelligence quotients consonant to a marked reduction in seizures. The improvement in intelligence rating was not confined to any

history of having been treated in a tuberculosis sanatorium for 18 months a few years before. While examination of the chest and of the sputum was negative, it is conceivable that tuberculosis may have accounted for the rapid sedimentation rate.

Of the five cases with a definitely elevated rate (over 30 millimeters in one hour) three were discharged as cases of simple obesity; two were discharged with the diagnosis of psychoneurosis. One of the patients with a diagnosis of psychoneurosis on discharge gave a history of painful swellings of the shoulder, arm, and hand, which had disappeared shortly before admission. The other patient was apparently normal except for what was thought to be a benign essential hypertension.

Of the 15 women with slightly elevated sedimentation rates, nine were discharged with a diagnosis of obesity, five as psychoneuroses and one with no evidence of disease. Of the cases of obesity, one gave a history of a subsiding thrombophlebitis on admission, and another was subsequently found to have been eight weeks' pregnant at the time of study. Of the five discharged as psychoneuroses, one showed diverticula of the colon, another had mild hypochromic microcytic anemia, and a third had a mild synovitis of the right wrist. The fourth patient had undergone extensive dental extractions a few weeks before admission, and the fifth had a fracture of the tibia, which had been reduced two weeks before admission. The patient discharged without evidence of disease was recovering from a severe infection of the upper respiratory tract at the time of admission.

Therefore, of the 21 cases with increased sedimentation rates, but without evidence of disease, detailed study of the records raised some doubt as to the absolute lack of explanation in 11 cases. The other 10 were considered to be cases of simple obesity. There is no apparent association of obesity and increased sedimentation rate, but the coincidence is noted.

*Relationship of the Actual Sedimentation Rate to the Expected Rate.* Certain organic diseases seldom produce an increase in the blood sedimentation rate. Other diseases, usually found to have an increase in the sedimentation rate, may be present in a given case without acceleration of the sedimentation rate. For example, a patient with rheumatic heart disease, but without evidence of rheumatic activity, would be considered to have a disease in which the sedimentation rate would be expected to be normal. For practical purposes, such a diagnosis might be considered a negative diagnosis in so far as the sedimentation rate was concerned.

Accordingly, the group of 1549 cases previously designated as having shown evidence of organic disease was subdivided into a group in which evidence of a disease usually associated with an increased sedimentation rate was discovered, and a group in which evidence of such a disease was lacking. The general table, as compiled by Cutler,<sup>2</sup> and modified by Bannick,<sup>10</sup> was used as a basis for this division. Consideration was also given to the findings of other authors, who studied the sedimentation rate in specific diseases. In general, accelerated rates were expected in chronic and

favorable influence on intelligence or learning ability, and remarked that the intelligence ratings in his group of cases have been as good as, if not slightly better than, tests made in previous years.

Perhaps a little more weight can be attached to the raising of the performance quotient in nine patients while it was lowered in only three in spite of the fact that seizures were reduced in all of them. Probably the effect of the drug in lessening seizures, promoting confidence, a feeling of well-being, alertness, and initiative "removed the brakes," so to speak, from the patient's latent performance ability and gave a truer index of his capacity.

### SUMMARY AND CONCLUSIONS

Twenty-nine chronic idiopathic epileptics and 44 patients with symptomatic epilepsy who have received dilantin sodium over a period of 12 to 18 months were observed from the standpoint of the drug's value in controlling seizures, its influence on conduct, its effect on psychometric ratings, and its relative value in the different groups of epilepsy.

1. About 65 per cent had a very marked reduction of seizure incidence.
2. About 50 per cent showed an improvement in conduct. This occurred in patients who had a pronounced diminution in the number of seizures, but as many showed no such improvement despite an equal reduction of attacks. We do not attempt to explain this fact.
3. There was no significant influence on intelligence ratings.
4. Performance ratings were raised appreciably in a small percentage of patients. The drug seemed to have a greater beneficial effect in this capacity than on intelligence.
5. There did not appear to be a definitely greater responsiveness to the drug by one group of epileptics over another.

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in specific diseases show invariable increase in the sedimentation rate in any single disease. Even in active pulmonary tuberculosis, 7.35 per cent of 2,000 cases showed a normal sedimentation rate.<sup>13</sup> The following cases are examples of those in which an elevated rate was expected, and a normal rate obtained.

*Case 1.* L. O., a widow, aged 59, entered the Diagnostic Hospital on January 25, 1937. She had been in good health prior to July 1935, when she noticed a mass in her left breast. One year later she consulted a physician; a radical mastectomy was performed; and the structure of the growth showed it to be scirrhous carcinoma. In November 1936, four months after the operation, she noted several masses in the region of the scar. There had been no weight loss, or other complaints.

Examination revealed numerous hard, non-tender, nodular masses lying along the operative scar. There was no localized tenderness. There were several small, firm, supraclavicular nodes on the left. The examination was otherwise negative, and no evidence of other metastases was noted. There was no anemia. The blood sedimentation rate was 5 millimeters in one hour. (Incidentally, many of our unexpectedly normal rates appeared in patients with cancer.)

*Case 2.* I. L., a single male, aged 29, was admitted to the Diagnostic Hospital on Oct. 11, 1932, complaining of slight non-productive cough, a loss of 10 lbs. in weight, easy fatigability, and increased irritability. A year and a half previously he had been told that he had an arrested tuberculosis. Physical examination was negative with the exception of evidence of weight loss. Roentgen-ray examination of the chest showed a moderately extensive parenchymal involvement at the apex of the right lung. There was no clinical or laboratory evidence of activity. The blood sedimentation rate was 2 millimeters in one hour on two occasions. He gained 20 pounds during one month, and was discharged.

He returned to the Hospital on June 2, 1937. He had been well until a few months before admission, when he had an occasional slight elevation of temperature. The physical examination was again negative. Roentgen-ray examination showed an active lesion in the apex of the left lung, which had not been present at the time of the first examination. Over a period of two months this infiltration showed definite regression, confirming the diagnosis of an active process at the time of admission. The blood sedimentation rate was not above four millimeters in one hour, on four determinations.

There were, of course, cases in which the sedimentation rate was elevated, but a normal sedimentation rate would have been predicted following the admission history and physical examination. In many cases this fact led to a more extensive search, and evidence of a disease usually associated with an increased sedimentation rate was found. It is in just these cases that the routine blood sedimentation test is of great help, since an unexpectedly elevated rate leads to a more intensive search for evidence of disease.

*Significance of an Elevated Sedimentation Rate in Relationship to the Type of Disease.* Elevation of the blood sedimentation rate in a case in which there is no evidence of an organic disease usually associated with such an increase may be as misleading as an elevated rate in a case without evidence of disease. In our series there were 738 cases of organic disease of a type usually associated with a normal sedimentation rate. In this group

rate, determined on blood obtained on the first morning of hospitalization, the patient having been without food for at least eight hours. The test was begun within 30 minutes of the time of the collection of the blood. The

TABLE I  
Age and Sex Distribution of Cases

Age	Male	Female	Total
1-10	8	4	12
11-20	92	119	211
21-30	124	176	300
31-40	153	202	355
41-50	196	233	429
51-60	217	183	400
61-70	156	125	281
71+	44	31	75
Totals	990 48%	1073 52%	2063

tube was not allowed to vary from the exact vertical position; the rack stood at room temperature; and the rate was determined at the end of 20 minutes, one hour, and two hours.

In this study the one hour determination was considered to be the significant value. The 20 minute figure was helpful in discovering certain technical errors, leaking and clotting. The two hour determination was useful as a check on the one hour figure. Except in cases showing a very rapid rate, the sedimentation at the end of one hour represented from 40 to 60 per cent of the value at the end of two hours. In a few cases the one hour level amounted to 20 per cent or less of the two hour figure. In these cases, a repetition of the test gave the more usual relationship.

*Normal Values.* There is no complete agreement as to the normal sedimentation rate, even by the same method of determination. Westergren<sup>6</sup> in 1921 expressed the opinion that a rate of 10 millimeters in an hour was definitely pathological. In our series a sedimentation rate of more than 20 millimeters in one hour has been considered abnormal. The selection of this value was based upon a consideration of the literature and the experience of those who studied these individual cases. It corresponds independently to the value advocated by Bannick et al.<sup>8</sup> Arbitrarily, the cases were divided into the following groups.

*Group I.* Normal Sedimentation Rate—rates from zero to 15 millimeters at the end of one hour.

*Group II.* Borderline Sedimentation Rate—rates from 16 to 20 millimeters at the end of one hour.

*Group III.* Slightly Elevated Sedimentation Rate—rates from 21 to 30 millimeters at the end of one hour.

the sedimentation rate had increased to 43 millimeters in an hour. Four days after admission he was feeling perfectly well, the temperature and white blood cell counts were normal, but the sedimentation rate remained unchanged. On the fifth day roentgen-ray examination of the gastrointestinal tract showed no unusual findings, but the sedimentation rate had risen to 65 millimeters in one hour. He was discharged with a diagnosis of subsiding appendicitis and was kept under observation.

On May 5, one week after discharge, he was feeling well. There was slight leukocytosis, and the sedimentation rate was 36 millimeters in one hour. On May 28, his appendix was removed. There was no evidence of other intra-abdominal disease, and the appendix showed changes in structure consistent with a diagnosis of subsiding acute inflammation.

The patient has remained well up to the present time. It has been emphasized by Lesser and Goldberger<sup>15</sup> that the sedimentation rate in appendicitis is not increased, and no evidence of other disease usually associated with an increased sedimentation rate was discovered in this case.

*The Sedimentation Rate in Cases in Which Other Routine Laboratory Procedures Were Negative.* Certain cases showed normal results on all of the following routine laboratory procedures: Hinton, Wassermann, and Kahn tests, urinalysis, and white blood cell count. These cases, 1063 in all, were divided into "positive" and "negative" groups according to diagnosis, and the blood sedimentation rates were related to the two groups, as shown in table 5.

TABLE V  
Relationship of the Sedimentation Rate to the Diagnosis in Cases in Which Other  
Routine Procedures Were Negative

Sex	Sedimentation—mm. per hr.				Total Cases	Total Elevated Rates
	0-15	16-20	21-30	31 +		
Diagnosis Positive						
Male.....	187 55.9%	36 10.7%	34 10.1%	77 23.3%	334	111 33.4%
Female.....	181 52.7%	47 13.7%	52 15.1%	63 18.5%	343	115 33.6%
Totals.....	368 54.3%	83 12.2%	86 12.7%	140 20.8%	677	226 33.5%
Diagnosis Negative						
Male.....	146 95.4%	6 3.9%	1 0.7%	0	153	1 0.7%
Female.....	212 91.0%	12 5.1%	6 2.6%	3 1.3%	233	9 3.9%
Totals.....	358 92.7%	18 4.6%	7 1.8%	3 0.9%	386	10 2.7%

however, was present in some portion of the cases classified as "positive." Table 3 shows the distribution of the cases according to these groups, and the sedimentation rates in each group.

TABLE III  
Distribution of the Sedimentation Rates in Relation to Diagnosis

Sex	Sedimentation—mm. per hr.				Total Cases	Total Elevated Rates
	0-15	16-20	21-30	31 +		
Diagnosis "Positive"						
Male . . . . .	380 47.5%	67 8.3%	98 12.3%	255 31.9%	800	353 44.2%
Female . . . . .	330 44.1%	91 13.6%	109 14.7%	219 27.6%	749	328 42.3%
Totals . . . . .	710 45.9%	158 10.2%	207 13.3%	474 30.6%	1549	681 43.9%
Diagnosis "Negative"						
Male . . . . .	180 94.8%	9 4.7%	1 0.5%	0	190	1 0.5%
Female . . . . .	281 86.7%	23 7.0%	15 4.8%	5 1.5%	324	20 6.3%
Totals . . . . .	461 89.7%	32 6.2%	16 3.1%	5 0.9%	514	21 4.0%

*Significance of an Elevated Sedimentation Rate in Diagnosis.* In the group of cases in which no evidence of organic disease was discovered, there were five cases in which the sedimentation rate was more than 30 millimeters in one hour, and 16 cases in which it was between 21 and 30 millimeters. In Cutler's series<sup>2</sup> of 177 cases with an elevated rate, only eight cases showed no disease (4.5 per cent). Wintrobe<sup>5</sup> also mentioned that there were 31 of 136 cases (22.7 per cent) in which increased sedimentation rates were present, and were not adequately explained by the findings on examination of the patient. However, many of his patients were seen on only one occasion. Gallagher<sup>4</sup> reported five cases among 685 (0.7 per cent) in which there was an unexplained, slightly accelerated rate. Schattenberg,<sup>3</sup> on the other hand, found that some disease process was the cause for every accelerated sedimentation rate.

The records of these 21 patients without evidence of organic disease but with an increased sedimentation rate were subjected to a more careful study. The most striking fact was the presence of only one male in the group. He was found to have a sedimentation rate of 23 millimeters in one hour, and was discharged as a case of unclassified psychosis. However, he gave a



tion rates in these cases were related to the degree of anemia, and the results were tabulated in table 6.

In the group of 186 cases showing a definite anemia, 69 cases, 37 per cent, showed a normal sedimentation rate. Even 7 of the 18 cases showing

TABLE VI  
Relationship of the Sedimentation Rate to the Red Cell Count in Cases  
with Anemia

Red Cell Count	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81+	Total
3,500,000 to 3,100,000...	24	17	11	6	3	12	5	2	15	95
3,000,000 to 2,600,000...	5	8	10	4	1	3	3	0	10	44
2,500,000 to 2,100,000...	3	5	4	0	4	1	4	0	8	29
2,000,000 and below....	2	5	1	3	1	1	1	0	4	18
Totals.....	34	35	26	13	9	17	13	2	37	186

a red blood cell count of less than two million cells per cubic millimeter showed a normal sedimentation rate. These findings represent a strong argument against the necessity for the correction for anemia when the sedimentation test is used as a routine procedure. The following cases are examples of this group.

*Case 5.* W. T., a white male, aged 66, was admitted to the Diagnostic Hospital on October 18, 1937, complaining of loss of appetite, weakness and jaundice of six months' duration. Examination revealed a stuporous, emaciated, icteric, pallid man. There was absence of the vibratory sense over the lower extremities; the tongue was smooth and red; and the spleen was not palpable. Laboratory studies showed a histamine achlorhydria, a red blood cell count of 980,000 cells per cubic millimeter, and a hemoglobin level of 4.6 grams per 100 cubic centimeters of blood. There were numerous macrocytes, and the red blood cells were hyperchromic. The serum proteins were 3.66 per cent, albumin 2.28 per cent, and globulin 1.38 per cent. The mean corpuscular volume was 113 cubic micra. The blood sedimentation rate was 7 millimeters in one hour. He improved steadily under appropriate therapy with liver extract.

*Case 6.* M. L., a white widow, aged 54, was admitted to the Diagnostic Hospital on September 1, 1937. Over a period of 18 months she had gradually developed weakness, anasarca and orthopnea. Her diet had been grossly deficient, consisting largely of bread, potatoes, and rice for two years. Examination revealed a pallid, dyspneic, edematous woman. There was slight cardiac enlargement, marked edema of the feet and ascites. There were 1,560,000 red blood cells per cubic millimeter of blood, and the hemoglobin level was 2.5 grams per 100 cubic centimeters of blood. The mean corpuscular volume was 75 cubic micra. The blood sedimentation rate was 18 millimeters in one hour. She showed striking improvement, with an adequate diet and iron.

*Relationship of the Sedimentation Rate to the White Blood Cell Count.* There is general agreement that variations in the total leukocyte count bear no direct relationship to the sedimentation rate; but the average count is often slightly higher in cases with a rapid rate, because of the relationship of both

acute infections, malignancy, localized suppurations, and tuberculosis. Normal sedimentation rates were expected in simple catarrhal inflammations, chronic ulcerations, metabolic diseases, chronic valvular disease of the heart and allergic diseases. Table 4 shows the result of this division, and the relationship of the blood sedimentation rates to each of these groups.

TABLE IV  
Relationship of the Expected Sedimentation Rate to the Actual Rate

Sex	Sedimentation—mm. per hr.				Total Cases	Total Elevated Rates
	0-15	16-20	21-30	31 +		
Normal Sedimentation Rate Expected						
Male.....	293 81.6%	35 9.7%	27 7.5%	4 1.2%	359	31 8.7%
Female.....	278 73.1%	48 12.6%	42 11.0%	12 3.3%	380	54 14.3%
Totals.....	571 77.2%	83 11.2%	69 9.3%	16 2.3%	739	85 11.6%
Increased Sedimentation Rate Expected						
Male.....	87 19.7%	32 7.2%	71 16.1%	251 57.0%	441	322 73.1%
Female.....	52 14.1%	43 11.7%	67 18.1%	207 56.1%	369	274 74.2%
Totals.....	139 17.1%	75 9.4%	138 17.0%	458 56.5%	810	596 73.5%

There is general agreement that a normal sedimentation rate does not rule out disease. In our series 868 cases, 56.1 per cent of the 1549 cases with evidence of an organic disease, showed a normal sedimentation rate. Even in the group of 810 cases with evidence of an organic disease usually associated with an increased sedimentation rate, 214 cases, 26.5 per cent, showed a normal rate. These findings are not entirely in agreement with other reports in the literature. Hirsh,<sup>11</sup> in a series of 205 determinations in cases in which the blood sedimentation rate was expected to be elevated, reported that every case showed an elevated rate. Wintrobe<sup>12</sup> expressed the opinion that normal rate was rarely found in the presence of organic disease. In 444 cases in which the corrected sedimentation rate was normal, manifest organic disease was found in only eight instances (1.8 per cent). However, he mentioned high values in a number of cases of infection in which a slight increase was expected. Cutler<sup>2</sup> also stressed the rarity of the normal sedimentation rate in the presence of clinically active disease. On the other hand, few of the studies dealing with the sedimentation rate

loss of weight, and numerous other symptoms. The upper abdominal pain was the most constant symptom, coming on about five minutes after the taking of food. Tiredness was so marked that it was not alleviated by 18 hours of sleep. He had not been well since 1912, and had developed abdominal pain as early as 1918. Physical examination showed obesity and, with the exception of slight lower abdominal tenderness, was negative. The diagnosis at this time was psychoneurosis.

The urine was normal, and there was no anemia. All other studies, including roentgen-ray examination of the gastrointestinal tract, were negative. The blood sedimentation rate was 58 millimeters in one hour, and remained above 50 millimeters on four subsequent determinations. He complained of severe abdominal pain throughout the period of observation, but without definite physical findings. He was discharged on May 3, 1935. It was thought that most of his symptoms were due to psychoneurosis, but, because of the increased sedimentation rate, the question of retroperitoneal abscess or neoplastic growth was raised, and an interval study was advised.

Two days after discharge, the patient experienced more severe abdominal pain, and a mass was palpated in the left upper quadrant of the abdomen. Laparotomy showed a large carcinoma of the tail of the pancreas which involved the neighboring peritoneum and contained a large recent hemorrhage.

*Case 8.* E. L., a Russian male, aged 47, was admitted to the Diagnostic Hospital on May 25, 1933 complaining of abdominal cramps. He had noticed abdominal distention and slight lower abdominal pain 12 weeks before admission. The pain had become more troublesome during the nine days before admission. He had lost his job six months previously and had been drinking rather heavily since that time. Physical examination was negative with the exception of upper abdominal tenderness which disappeared when his attention was distracted. There was no anemia or leukocytosis. The blood sedimentation rate was 41 millimeters in an hour. He wept at the prospect of returning home. He was discharged on June 1, 1933, with the diagnoses of psychoneurosis and essential hypertension.

Three days after discharge, the abdominal pain became more severe and he was admitted to another hospital. Examination and laboratory studies were similar to the previous studies, but the blood sedimentation rate was not determined. The emotional instability was marked and it was concluded that much of his unhappiness was of psychic origin. The white cell count was found to be 20,000 per cubic millimeter. He died on June 7, 1933, four days after admission. Postmortem examination showed thrombosis of the superior mesenteric artery with gangrene of the ileum. The thrombus showed organization, old and recent. There was also an organized thrombus of the inferior mesenteric artery, with infarction of the small and large bowel.

### SUMMARY

The blood sedimentation test was used as a routine laboratory procedure in 2063 unselected cases of general diagnostic problems. A modified Westergren technic was employed; the reading at the end of one hour was considered to be the significant reading; the rate was not corrected for anemia; and a rate of more than 20 millimeters in one hour was considered abnormal. The presence of organic disease was indicated in 702 cases, or 34.1 per cent of the series, by a sedimentation rate which was elevated.

Of all the cases with definite evidence of organic disease (1549), 43.9 per cent, or 681, had elevated rates. Of those cases without evidence of organic disease (514), only 4.0 per cent had elevated rates. Because cer-

85 cases, 11.6 per cent, showed an increased sedimentation rate. In a similar group of cases, Hirsh<sup>11</sup> reported that of 283 determinations that should have given a normal rate, only 11 (3.8 per cent) showed accelerated rates. Wintrobe<sup>12</sup> observed that in a number of instances of infection in which slight or moderate increases were expected, high values were obtained.

The records of the 16 patients with definitely elevated rates were reviewed. The fact that only four were males is again striking. Of the 16 cases, organic disease was present in 14. One patient was a 14 year old girl, discharged with a diagnosis of "lumbago," and the second will be discussed in more detail below. Of the remainder, 12 were discharged with a diagnosis of either hypertensive cardiovascular disease, or arteriosclerotic heart disease. Cases of this type were placed in the group in which rapid sedimentation rates were not expected largely on the basis of the variation of opinion as to the expected rate, as summarized by Wood.<sup>14</sup> Certainly some of these cases belong in the group in which rapid rates would be expected, according to his findings.

As noted above, an increased sedimentation rate occurred in 21 cases in which no evidence of organic disease was discovered, and in 85 cases in which evidence of an organic disease usually associated with a normal sedimentation rate was found. These two groups represent 106 cases, 5 per cent of the series, in which an increased sedimentation rate was misleading. Therefore, in our series, a sedimentation rate of more than 20 millimeters in one hour was indicative of an organic disease of a type usually associated with an increased sedimentation rate in 95 per cent of the cases. The following examples are representative of the group in which no evidence of an organic disease usually associated with an increased sedimentation rate was discovered, but in which the rate was increased.

*Case 3.* D. S., a widow, aged 67, entered the Diagnostic Hospital on April 30, 1934, complaining of abdominal pain following meals, which had been present for one year. There had been occasional vomiting, constipation, dyspnea on exertion, and nocturia for several years. There was slight upper abdominal tenderness, and the blood pressure was 210 mm. mercury systolic and 120 mm. diastolic. The red blood cells numbered 3.7 million per cubic millimeter of blood, and there was slight leukocytosis. The urine contained a small amount of albumin. Study of the colon following a barium enema showed diverticuli of the sigmoid colon. Study of the stomach, small intestine, and gall-bladder was negative. The blood sedimentation rate was 118 millimeters in one hour. She was discharged on May 16, 1934. None of the findings would explain such a greatly elevated sedimentation rate.

*Case 4.* V. L., a single male, aged 38, was admitted to the Diagnostic Hospital on April 24, 1936 complaining of pain in the lower abdomen. Two days before admission he developed mid-abdominal pain which shifted to the right lower quadrant of the abdomen. There had been no nausea, and several bowel movements followed a laxative. On admission the temperature was 99.2 degrees; there was a moderate leukocytosis; and the sedimentation rate was 39 millimeters in one hour. There was local tenderness on pressure in the right lower quadrant of the abdomen.

He was observed for several days. On the second day the temperature was normal; the pain had disappeared; and the white blood cell count had declined. However,

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20. CUTLER, J. W., PARK, R. W., and HERR, B. S.: The influence of anemia on blood sedimentation, *Am. Jr. Med. Sci.*, 1938, cxcv, 734-751.
21. YARDUMIAN, K.: Physicochemical factors influencing the red cell sedimentation rate, *Am. Jr. Clin. Path.*, 1937, vii, 105-119.

The blood sedimentation rate was elevated in 226 of the group of 1,063 cases showing negative results on other routine laboratory procedures, 10.9 per cent of the entire series. It seems reasonable to conclude that, in these cases, the presence of disease would have been overlooked, from a laboratory standpoint, if the blood sedimentation test had not been performed as a routine diagnostic procedure. Ten cases of the group, 0.5 per cent of the entire series, showed an increased rate but no discovered evidence of organic disease.

*Relationship of the Blood Sedimentation Rate to Anemia.* In recent years much emphasis has been placed on the necessity for correction of the sedimentation rate for anemia. Several methods for determination of the sedimentation rate have been advocated because of the relative ease with which they may be corrected for anemia.<sup>10, 17</sup> There is agreement that, in general, the sedimentation rate bears an inverse proportion to the volume percentage of the red blood cells. Wintrobe<sup>5</sup> and Bannick et al.,<sup>8</sup> among others, have pointed out that the "corrected" sedimentation rate may be misleading, in a case in which the uncorrected rate may be given a more nearly correct index of the condition of the patient. Gregg<sup>18</sup> reported the results of sedimentation tests on rabbits made anemic by bleeding, and found that they were less rapid than the values derived from the dilution experiments upon which charts for correction of the sedimentation rate for anemia are based. Bannick et al.<sup>8</sup> observed that the sedimentation rates in cases of bleeding from duodenal ulcer were usually not increased as much as the degree of anemia would have led one to expect. Bouton<sup>19</sup> concluded that in a case with anemia with essentially normal findings otherwise but with a definitely pathological sedimentation curve, the true disease had not been determined and was of serious nature. He also advanced the interesting idea that correction for anemia gives a false accuracy to a procedure which is essentially non-specific and which yields only approximate values. Cutler et al.<sup>20</sup> concluded from a critical appraisal of both experimental and clinical observations that anemia has little to do with the phenomenon of blood sedimentation. Our findings are in agreement with this statement.

The sedimentation rates in our series had not been corrected for anemia. The non-specific nature of the phenomenon had been recognized, and the blood sedimentation test had been considered as something of a "laboratory impression." In a diagnostic study the presence of anemia was considered to be of importance, either as the primary disease or as a manifestation of the primary disease. Therefore, a rapid sedimentation rate reflecting the presence of anemia alone is of importance when the test is used as a routine procedure. Also, the added complexity of the test, if correction of anemia is considered essential, is probably responsible in part for the infrequency with which the test is used as a routine laboratory procedure. In our series of cases there were 186 cases showing a definite anemia, that is, with less than 3.5 million erythrocytes per cubic millimeter of blood. The sedimenta-

but also of such habits as hours of sleep, exercise, and the time of meals. Indeed, it is likely that the process of adjustment involves not only the metabolic activities, but also, to some extent, the functions of digestion which are so responsive to regularity of routines.

Despite its sluggishness, physiological adjustment usually begins promptly, if a correct dietary formula has been instituted, and an improving glucose tolerance may be evident within 24 to 48 hours. But, this improve-

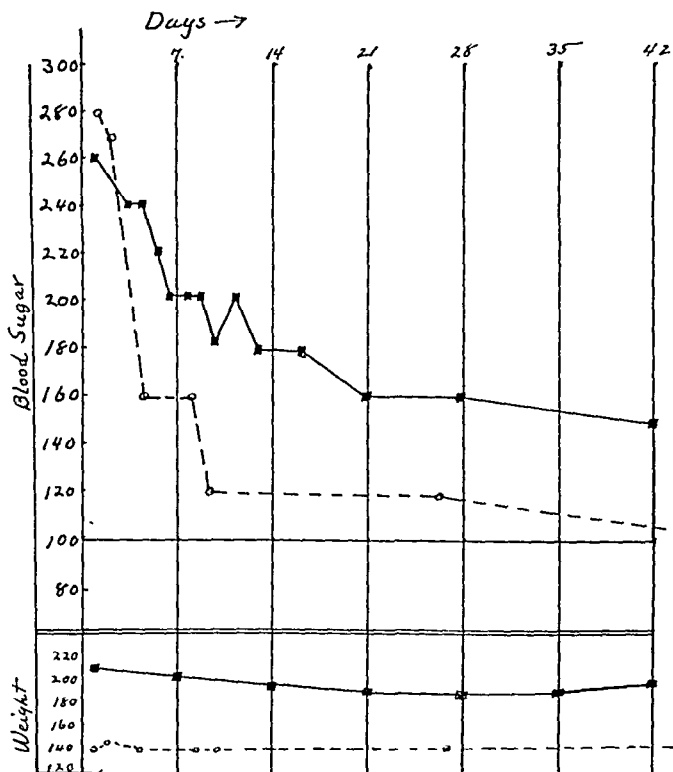


FIG. 1. Blood sugar levels of two patients under almost identical dietary régime; no insulin.

○---○ = K., female, aged 60;

diet: C.H. 120, Prot. 65, Fat 90; calories 1550

■—■ = B., female, aged 72;

diet: C.H. 115, Prot. 65, Fat 100; calories 1620.

In both cases the diet remained unchanged throughout the above recorded periods. Note the difference in the rate of the "physiological adjustment," "K" being more rapid, despite the fact that she presented more severe symptoms at the beginning of treatment.

ment is only a beginning, and if the carbohydrate intake is maintained unchanged, the blood sugar levels will show a further downward trend until the adjustment is completed, the time required for this varying from two or three days to as long as several weeks. While this downward trend is usually a steady one, with the utilization of glucose a little better each day, in occasional cases the improvement seems to take place in a series of abrupt steps, each after several days of more or less stationary conditions. Whether the adjustment proceeds smoothly, or by a series of steps, one can recognize

factors to a number of diseases.<sup>21</sup> This partial parallelism has been used as an argument against the need for the use of the sedimentation test as a routine procedure.

The cases in this series were divided into a group in which the white blood cell count was elevated and another in which the white cell count was normal. A count of more than 10,000 leukocytes per cubic millimeter of blood was considered abnormal.<sup>22</sup> The sedimentation rates of the two groups of cases were then tabulated, and the results are shown in table 7.

TABLE VII  
Relationship of the Leukocyte Count and Sedimentation Rate

W.B.C. Count per Cubic Millimeter	Sedimentation Rates—mm. per hr.				Total Cases	Total Cases Elevated Rates
	0-15	16-20	21-30	31 +		
10,000 or above.....	233 45.3%	40 7.7%	57 11.1%	184 35.9%	514	241 47.0%
Below 10,000.....	938 60.5%	140 9.0%	176 11.3%	295 19.2%	1549	471 30.5%

This study showed that 47 per cent of the cases with an increased white cell count showed an increased sedimentation rate. However, 30 per cent of those with a normal white cell count showed an increased rate. This indicates that the apparent parallelism between increased sedimentation rate and increased white cell count is not sufficiently marked to permit the exclusion of the one test when the other test is performed routinely.

*Relationship of the Sedimentation Rate to Sex.* In considering the normal sedimentation rate, it was formerly customary to assign a slightly higher rate to women than to men.<sup>7</sup> Rourke and Ernstene<sup>18</sup> expressed the opinion that the faster rate in women was due to the lower normal hematocrit value. Wintrobe<sup>17</sup> also stated that the difference was due largely to quantitative difference in the total number of cells. Our observations develop one further fact as regards the sedimentation rates in males and females, namely, that among females there are more misleading accelerated rates than among males. In all, 32 males, 3.2 per cent of the series, showed an increased rate when no evidence of an organic disease usually associated with an increased rate was discovered. Among the females, however, there were 74 such cases, 6.9 per cent of the group.

*The Sedimentation Rate in Occult Disease.* One of the most important reasons for the use of the sedimentation test as a routine procedure is that it may call attention to the presence of more or less occult disease. The following cases are illustrative:

*Case 7.* M. P., a white, married male, aged 39, was admitted to the Diagnostic Hospital on April 27, 1935, complaining of pain in the back, abdominal pain, tiredness,



It is not within the purpose or scope of this paper to discuss in any detail the various theories that might explain this time lag in the metabolism of carbohydrates in diabetes. However, there are several well recognized features of the carbohydrate metabolism in normal individuals that probably have a direct bearing on this matter, and are therefore presented very briefly and without any attempt to refer to the extensive literature on the subject. These features are: First, the presence of glucose in the blood, or body fluids, apparently acts as either a stimulus or an aid to the utilization of glucose. This effect is evident under the following conditions: (*a*) in an ordinary glucose tolerance test the blood sugar will drop in two to four hours to a level considerably lower than it was just before the glucose was administered. Occasionally this drop is sufficient to cause a mild hypoglycemic reaction. Indeed, mild diabetics seem to be especially prone to these hypoglycemic reactions after taking an unaccustomed amount of carbohydrate. (*b*) After prolonged fasting (three to five days) ingestion by a normal individual of an average amount (50 gm.) of glucose will result in an abnormally high rise in the blood sugar (200 mg. or even more). Apparently, during the prolonged fast, throughout which there is characteristically a low blood sugar, the mechanism for the utilization of glucose is partially lost and is not immediately recovered on the sudden appearance of glucose in the blood. (*c*) Again, if two successive doses of glucose are given, one or two hours apart, the rise of the blood sugar following the second dose is much less marked than that following the first. (*d*) Finally, a sustained, excessive demand on the carbohydrate utilization processes eventually causes their exhaustion, with a corresponding reduction in the glucose tolerance.

These well known features of the response to glucose ingestion indicate that the presence of glucose in the blood activates some mechanism for the removal of glucose from the blood; and, when this mechanism is partially lost by disuse, as in starvation, it requires an appreciable time to be brought into full play. Moreover, this mechanism can be exhausted by over-stimulation by as excessive glucose in the blood, and when thus exhausted, recovery is slow.

Second: a further and perhaps even more important element in the time factor in carbohydrate metabolism is found in the complex nature of the processes, in which the rôle of insulin is not entirely understood. Apparently there is an interaction between the pancreas, liver, adrenals, pituitary and tissues, calling for the elaboration of internal secretions and specific enzymes all of which enter into complex building up and breaking down of various forms of carbohydrate. In view of the interdependence of these internal secretions and the well known response of all glands to repeated, or "conditioning" stimuli, it is not surprising that a consistent but reasonable demand on the carbohydrate mechanism will result in a steady increase in sugar tolerance, but that when they are impaired, as in diabetes, ample

tain types of organic disease produce an increase in the sedimentation rate, while other types do not, these two general types of organic disease were separately analyzed. Of the cases with evidence of disease usually associated with an increased sedimentation rate, 73.5 per cent showed elevated rates. Those with evidence of a disease usually associated with a normal rate showed increased rates in 11.6 per cent. A normal sedimentation rate did not exclude the presence of the type of disease usually associated with an increased blood sedimentation rate. A sedimentation rate of more than 20 millimeters in an hour was indicative of organic disease of a type usually associated with an increased rate in 95 per cent of the cases. In 226 cases, 10.9 per cent, the blood sedimentation rate was elevated and other routine laboratory procedures were negative. Only 10 of these 226 cases had no discovered organic disease.

In a group of 186 cases showing anemia of less than three and one-half million red cells per cubic millimeter, 37 per cent showed a normal sedimentation rate. An elevated sedimentation rate and an elevated white blood cell count are not necessarily parallel findings.

The presence of an increased sedimentation rate in males showing no evidence of disease was noted in only one case. In general, an increased rate in the male was more likely to be present with a disease usually associated with an increased rate than in the female. The value of the routine use of the sedimentation test as an indicator of occult organic disease is noted.

### CONCLUSION

The blood sedimentation test performed by a simple method, without correction for anemia, is of value as a routine diagnostic procedure.

The author wishes to thank Dr. S. H. Proger for his advice and help in the analysis of these data, and the preparation of the manuscript.

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Therefore, with every change in the carbohydrate régime, the new formula should remain fixed for at least three or four days (barring emergencies) or longer if evidence of improvement continues. When the improvement ceases another change, if necessary, can then be made, this to be again followed by a period of watchful waiting. Such a policy of consistent, unhurried control offers the best chance of ultimate success in the treatment of diabetes.

# THE IMPORTANCE OF ALLOWING TIME FOR "PHYSIOLOGICAL ADJUSTMENT" IN ESTABLISHING THE DIET IN DIABETES \*

By R. R. SNOWDEN, M.D., F.A.C.P., *Pittsburgh, Pennsylvania*

THE term "physiological adjustment," as here used, refers to the way in which the physiological processes respond to the demands of carbohydrate metabolism. In the normal individual this adjustment is so prompt and efficient that even widely varying amounts of glucose are utilized almost immediately; in fact it is difficult to break through a normal glucose tolerance. In the diabetic, on the other hand, physiological adjustment is sluggish and lacks quick mobility; therefore, it can become fully effective only when the demands upon it are reasonable, and are maintained unchanged day after day until adjustment has had time to complete itself.

Several factors enter into this slowing up of the rate of physiological adjustment in the diabetic: the fundamental cause, of course, is the reduction in the capacity to utilize glucose. However, in previously untreated cases, another factor is superimposed in that the prolonged high blood sugar further depresses the already impaired glucose tolerance, and thus temporarily exaggerates the severity of the diabetes. Because of the variability of this second factor, it is almost impossible to determine the true severity of a case of diabetes in advance of treatment; and, for the same reason, the time required for physiological adjustment to a suitable régime cannot be predicted.

For example, in figure 1 are plotted the blood sugar determinations of two patients, under almost identical dietary régimes. One patient (Mrs. K.) responded unusually promptly, the blood sugar dropping to 160 in three days and on down to 120 in eight days from the beginning of the diet. The other patient responded much more slowly, requiring about three weeks to attain the tolerance that Mrs. K. showed in five days. And yet, curiously enough, Mrs. K., who responded so quickly, seemed to be a much more severe diabetic, as judged by the history, for she had lost weight, was bothered with polyuria, weakness, and itching, and had a sluggish ulcer on the ankle. Comparison of these two patients illustrates the variability of time for physiological adjustment, and the difficulty of predicting the severity of the disease.

Two conditions are essential if physiological adjustment is to develop in a favorable direction: (1) the diet must be reasonably close to the eventual tolerance of the patient, or, in the severe cases, to the insulin dosage; and (2) there must be consistent regularity day after day, not only of the diet,

\* Read at the Cleveland meeting of the American College of Physicians April 4, 1940.

explained on the basis that the result of alveolar distention is obliteration of the capillaries with obstruction to the flow of blood from the right to the left ventricle.

Investigations of the pulmonary circulation time in emphysema have been made in an effort to demonstrate the presence or absence of an increased resistance in the pulmonary circuit. Kountz, Pearson and Koenig<sup>6</sup> measured the circulation time through the lungs by injecting a dye into the right side of the heart of dogs with emphysema and recorded the interval of time before it appeared in a peripheral artery. They found no abnormal delay and concluded that there was no obstruction to the flow of blood through emphysematous lungs.

The studies of Weiss and Blumgart<sup>7</sup> were made by injecting a radioactive substance into the vein of one arm and measuring the interval before the emanation was detectable in the other arm. They found that only in far advanced cases of emphysema was the pulmonary circulation slowed. The conclusions drawn from these investigations are open to considerable doubt as far as their ability to indicate absence of resistance in the pulmonary circulation is concerned. It has been impossible as yet to prove a delay in the systemic circulation of patients with compensated hearts and systemic hypertension when an increased peripheral vascular resistance certainly exists. It, therefore, does not seem plausible to assume an absence of pulmonary circulatory resistance when the pulmonary circulation time is within normal limits. There is yet another factor which has not been studied adequately as a possible influence in the production of pulmonary hypertension in emphysema, that is the presence of arteriosclerosis of the pulmonary vessels. In recent years interest in what yet remains a relatively rare condition, namely, the so-called primary or idiopathic pulmonary arteriolar sclerosis has been increasing. From the evidence now available, there can be no doubt that advanced sclerosis of the smaller pulmonary arteries and arterioles can provoke marked pulmonary hypertension with subsequent right cardiac hypertrophy and failure.<sup>8</sup> The etiologic features of this condition, however, remain a controversial subject.

Steinberg<sup>9</sup> made a careful anatomic study of pulmonary arteriosclerosis and included in his report 50 cases of emphysema. An analysis of his tables reveals that sclerosis of the pulmonary vessels was present to a relatively high degree. Further studies by Miller,<sup>10</sup> Moschowitz<sup>11</sup> and more recently by Brenner<sup>12</sup> and by Kaltreider<sup>13</sup> indicate a rather frequent association of pulmonary arterial disease with advanced emphysema. This possible relationship between pulmonary emphysema and pulmonary vascular changes and their combined effect on the heart seemed worthy of additional investigation.

#### METHOD OF STUDY

The material for this study was selected from cases in which postmortem examination revealed essential emphysema. All cases in which the clinical

when it is complete by the fact that thereafter the blood sugar findings remain essentially the same day after day. It is only at this stage that one can judge whether or not a trial diet is suitable. If further changes are indicated, each change in the carbohydrate allowance is again followed by a period of physiological adjustment, which may be just as long as the preceding one. In brief, any change in the diet or insulin régime of a diabetic, whether the change is instituted at the beginning or in the midst of treatment, requires time for effective physiological adjustment; and the length of this time requirement cannot be predicted.

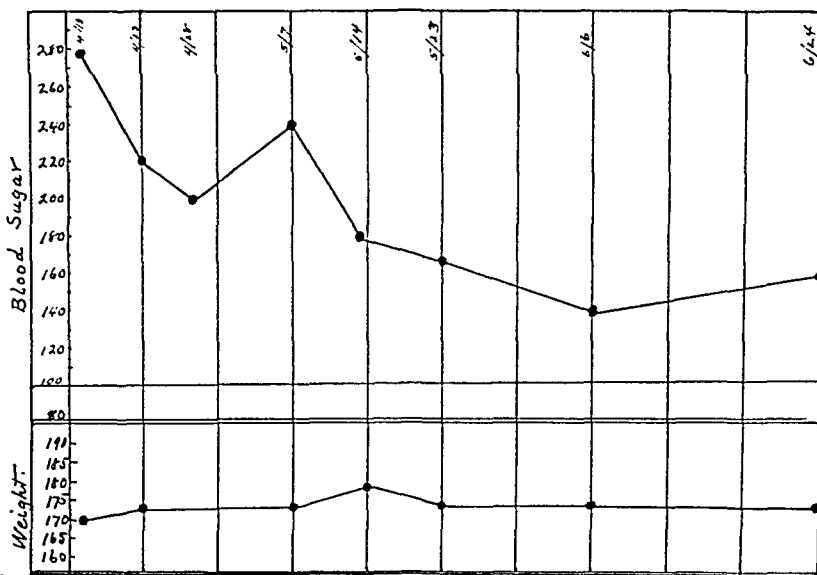


FIG. 2. Unusually slow "physiological adjustment."

Male, aged 57. Diet: C.H. 110, Prot. 80, Fat 100; calories 1660. Diet unchanged throughout the above period. No insulin.

An example of a fairly prolonged period of adjustment is shown in figure 2, the patient slowly developing an increasing tolerance, so that in four weeks he was utilizing practically all of an adequate diet, without insulin, and in six weeks his post-prandial blood sugar was normal. In this case the adjustment was unusually slow, but nevertheless the trend toward improvement was evident almost at once by the reduction in the blood sugars, taken in each instance one hour after lunch. The only treatment in this case was strict adherence to the diet (C.H. 110, Prot. 80, Fat 100; calories 1660), the patient continuing his ordinary business activities throughout. One can see that if the findings at the end of the first or second week had been accepted as the basis for further changes, insulin would probably have been given. Although the use of insulin prematurely would not have been disastrous in this case, it would certainly have resulted in additional weeks or even months of juggling of insulin and dietary formulae before eventual stabilization was attained.

degree of pulmonary emphysema noted at the time of postmortem examination. All grading was made on the basis of 1 to 4; grade 1 denotes a minimal degree of emphysema, and grade 4 the most marked degree with severe diffuse emphysema of both lungs.

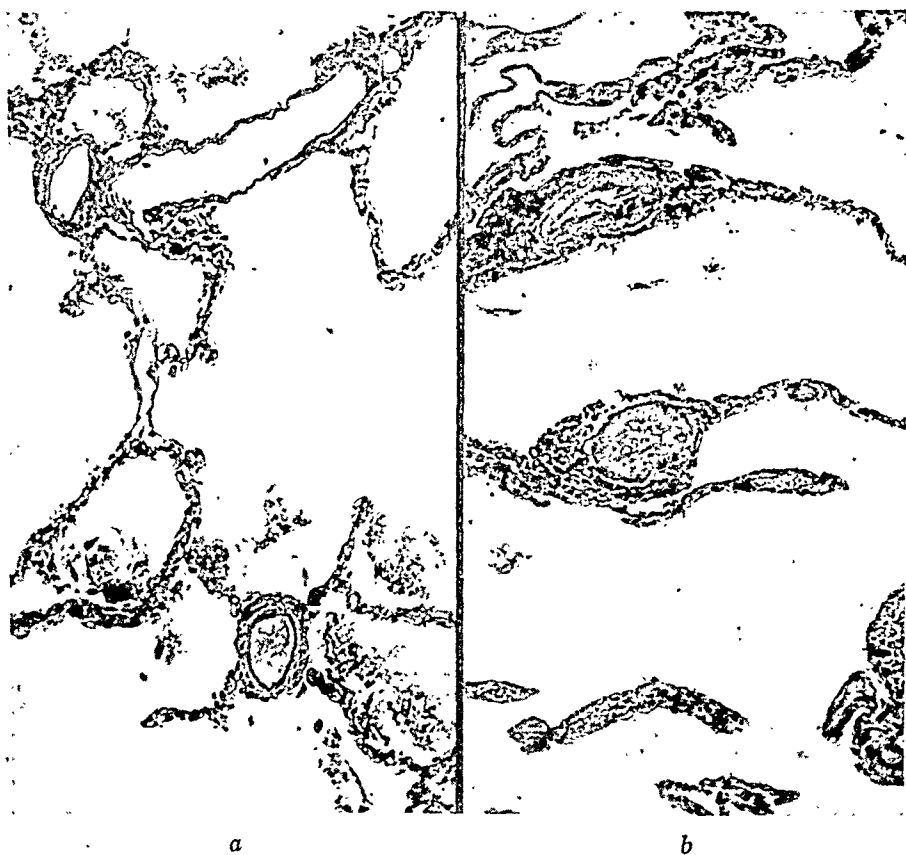


FIG. 1. Marked variation in the degree of arteriolar narrowing which may be found in the same case and in the same lung; *a*, normal arterioles in a section from the lung (hematoxylin and eosin,  $\times 125$ ); *b*, advanced pulmonary arteriolar sclerosis in section from the same lung as *a* ( $\times 90$ ).

Cases of emphysema of minimal degree, or grade 1, were not included in this study. It was thought advisable to select for study only cases in which the diagnosis of emphysema was interpreted by the pathologist as one of the essential anatomic diagnoses. Minimal degrees of emphysema with emphysematous blebs or minor degrees of compensatory or senile emphysema are a frequent finding at postmortem examination and their presence is of doubtful, if any, significance from the standpoint of respiratory or circulatory physiology; therefore, only cases of essential emphysema of grade 2 or more were studied. The ages of these patients ranged from 40 to 70 years.

The 32 cases reviewed were divided into three groups. The first group consisted of cases in which the degree of emphysema present was of moderate

time must be given for all these complex processes completely to adjust themselves to demands.

Whatever the metabolic background may be, the fact is that the time requirements of physiological adjustment must be given due consideration, if a correct dietary régime is to be worked out without confusion. One should proceed along some such system as the following: Begin with a diet based on the ideal weight, i.e., a diet which, if it could be utilized, would maintain the patient in a state of normal, healthy activity. Having established this ideal diet, it is adhered to without change, day after day, until its effects can be accurately evaluated. A daily record is kept of the body weight and urinary glucose (if any); and blood sugar determinations are made often enough to show their trend. On the basis of these data, one can usually judge within 48 hours whether or not physiological adjustment in a favorable direction will take place. As long as there is some improvement, as shown by a diminishing urinary glucose and dropping blood sugar, even though this be slight, no dietary change should be made. Indeed, if the utilization of glucose merely holds its own, one should wait at least a few days, to see if the adjustment might develop by a series of abrupt steps rather than the usual gradual adaptation.

In certain instances, of course, it will soon become evident that the diabetes is so severe that there is no hope of effective adjustment to the prescribed diet. The next step in these cases is to begin insulin, in a dosage based on the amount of glucose lost in the urine. With the institution of the insulin régime, the same policy of watching for signs of adjustment should be followed, for even when aided with insulin the metabolic processes adapt themselves to the new régime slowly, and to make changes prematurely in either the insulin dosage or the carbohydrate intake leads to confusion.

In all cases in which adjustment is proceeding in a favorable direction, or, to express it in another way, in which the glucose tolerance is rising, one cannot predict where the adjustment will stop. The rule should be to wait until improvement has ceased, as shown by a tolerance that is stabilized for several days or longer. Then, if the blood sugar is not within the normal limits, the necessary changes, whether in diet or insulin, are instituted, after which one again waits for effective adjustment to take place. It is evident that working out the correct diet for a diabetic requires not only observation and judgment, but, above all, patience, and that the rule "make haste slowly" is especially applicable.

### CONCLUSION

There is a very definite time requirement for a complete adjustment to any dietary change in diabetes. This time requirement varies from a minimum of three or four days to a maximum of as much as several weeks.



less other causes for cardiac disease are present. It may seem, therefore, that its frequent occurrence in this study demands further explanation. In most cases of pulmonary emphysema in which death occurs from congestive heart failure there are no doubt additional factors concerned, for with the fifth decade of life and beyond, arteriosclerotic and hypertensive heart disease is common and calcified relics of old healed valvular disease may be seen also. These factors may be more predominant than the emphysema in producing cardiac failure. Attempt was made, however, to eliminate from this study all cases in which there was any other cause for cardiac failure than emphysema. It is, of course, obvious that cases of coronary sclerosis could not be excluded, for its occurrence in greater or lesser degree in the period of life at which our material was obtained is universal. The possible presence of previous hypertension which was not recorded clinically must also be considered as a factor in the development of congestive failure in some of these cases. Regardless of this possibility, the occurrence of congestive heart failure in such a large number of cases in which there was no other evidence of heart disease and in which the degree of coronary sclerosis was negligible leads to the conclusion that advanced emphysema not only occasionally but in a high percentage of cases leads to ultimate failure of the heart.

*Weight of the Heart.* There was a significant increase in the weight of the heart above normal in all three groups. This increase in the weight of the heart, however, was not directly related to the severity of the emphysema, for the average increase above the calculated normal was greater in group 2 than in group 3 (table 1).

*Hypertrophy of the Right Ventricle.* There was a consistent increase in the frequency of occurrence as well as in the degree of right ventricular hypertrophy in the more advanced cases of emphysema. In the first group the right ventricle was enlarged in 65 per cent of the cases, in the second group in 87.5 per cent, and in the last group in 100 per cent. That there was a consistent increase in the average degree of right ventricular hypertrophy is shown by the fact that in group 1 the median grade of right ventricular hypertrophy was grade 1, in group 2 it was grade 2 and in group 3 it was grade 3 (table 1).

*Hypertrophy of the Left Ventricle.* Attention should be called to the fact that an appreciable hypertrophy of the left ventricle occurred in 11 cases (34 per cent) but in none of these was the enlargement of the left ventricle relatively greater than that of the right. The finding of both left and right ventricular enlargement has been noted in other studies. The question arises, why should there be any hypertrophy of the left ventricle in emphysema when from the theoretic standpoint the strain of the circulation is on the right ventricle alone. It has been suggested that there is a partial asphyxia of the heart muscle as the result of faulty exchange of oxygen in the lung. Experimental work by Vacek<sup>16</sup> and by Strughold,<sup>17</sup> seems to give some support to this contention. It would seem, however, that the

# PULMONARY EMPHYSEMA; A STUDY OF ITS RELATION TO THE HEART AND PUL- MONARY ARTERIAL SYSTEM \*

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THE effect of emphysema on the pulmonary circulation and its secondary influence on the heart continues to be a controversial subject. On the basis of the earlier necropsy examinations, the general opinion became well established that emphysema produced a barrier within the pulmonary circulation which led to hypertrophy of the right ventricle and frequently to congestive heart failure. This opinion gained general approval but in recent years considerable doubt has been raised concerning this previously established view. The historical background of this problem has been reviewed so excellently in a recent paper by Parkinson and Hoyle<sup>1</sup> that it is only necessary for me to cite a few of the more recent investigations.

Griggs, Coggin and Evans<sup>2</sup> found hypertrophy of the right ventricle in 30 per cent of the cases of emphysema studied. On the other hand, Alexander, Luten and Kountz<sup>3</sup> found little evidence of cardiac involvement in a clinical study of a series of 50 patients with asthma and emphysema of long standing. In a later paper, Kountz, Alexander and Dowell<sup>4</sup> stated that, by roentgenologic examination, enlargement of the heart was demonstrated in only eight of 66 cases of advanced emphysema. Parkinson and Hoyle examined 80 patients with emphysema with special regard to the size and silhouette of the heart as determined by roentgenologic methods. They found that the heart as a whole was not enlarged in cases of uncomplicated emphysema. Localized enlargement of the cardiac silhouette was noted in 40 per cent of the cases and involved most often the conus pulmonalis of the right ventricle. They concluded, however, that the cardiac factor in emphysema seldom is pronounced except late in the disease and then not always and not unless there is other associated cardiac disease.

It is interesting to note that from their roentgenologic study Alexander, Luten, and Kountz concluded that the cardiac factor in emphysema was negligible; yet in the more recent investigation by Kountz, Alexander, and Printzmetal<sup>5</sup> both right and left ventricular enlargement were found at necropsy in 10 of 17 cases of emphysema. After the experimental production of emphysema in dogs similar cardiac enlargement occurred.

If it is assumed that emphysema may produce strain on the right ventricle, it follows either that there is an increased resistance in the pulmonary vascular bed producing intrapulmonary hypertension or that the strain on the heart is consequent to a demand for an increased pulmonary circulation in an effort to overcome the defective error in ventilation. An increased resistance in the pulmonary circuit in emphysema long has been assumed and

\* Received for publication May 16, 1940.

nificant reduction, and in a few instances the average diameter of the lumen was more than that calculated for normal (tables 2 and 3).

In groups 2 and 3, which included the more advanced cases of emphysema, there was a greater incidence as well as a greater degree of narrowing in the arteriolar system. With the exception of a single case in group 3 in which there was no arteriolar obstruction, this relationship remained consistent.



FIG. 2. Emphysema of lung, grade 4.

To appreciate fully the importance of these changes in the arteriolar system it must be remembered that the pulmonary arteriolar bed, like the remainder of the vascular system, is endowed with a vascular reserve in excess of that necessary to meet ordinary functional demands. Experimental studies have demonstrated that as much as 50 per cent of the pulmonary circulation can be shut off without marked variation in the general

data gave evidence of hypertension, or the pathologic material evidence of valvular heart disease, pericarditis or other criteria of intrinsic heart disease which could have played a material part in determining the size and weight of the heart were discarded. In the cases selected for study the hearts were examined to determine the following data: weight and measurements of the thickness of the ventricles, including the minimal and maximal thickness of the muscle and the depth of the ventricles. From these measurements the degree of ventricular hypertrophy and dilatation was determined and recorded on the grading basis of 0 to 4 (grade 0 means no hypertrophy and is used for statistical purposes). The degree of coronary and aortic sclerosis was recorded.

The pulmonary artery and its main branches were studied grossly in all cases in which material permitted; in the other cases data as to the degree of gross pulmonary arteriosclerosis were obtained from the record of the necropsy. Sections from the different lobes of the lung were studied microscopically with regard to the pulmonary vessels. The degree of hypertrophy and thickening of the small muscular arteries was recorded, and representative arterioles from each section were selected and measured by means of a micrometer, according to the method of Kernohan, Anderson and Keith.<sup>14</sup> These measurements were compared to the ratio of normal wall to lumen in vessels of similar size, as determined by Kaump<sup>15</sup> in his study of normal pulmonary arterioles. By comparison of these figures it became possible to express the diameter of the lumen of each vessel as a percentage of that of the normal vessel and from all arterioles measured in each case the average diameter of the lumen is expressed as a percentage of that normally encountered. This figure, it is believed, best indicates the degree of narrowing or obstruction in the pulmonary arteriolar bed. Vessels in which the outside diameter was from 25 to 200 microns were considered as arterioles and are the ones included in these measurements.

It is well to mention at this point that on microscopic examination of the pulmonary arterioles marked variability was found with regard to the changes in the arteriolar walls. In some arterioles the increased diameter of the wall of the vessel was due predominantly to hyperplasia of the intimal layers whereas in others either in the same section or from the same lung hypertrophy of the media accounted for the increase in diameter of the wall. Furthermore these changes were not always symmetrical in a single vessel. A considerable variation in the degree of arteriolar narrowing also was noted in sections from the same case or even from the same lung (figures 1*a* and 1*b*). This fact is mentioned to emphasize the importance of the examination of several sections from the various parts of the lung and the careful measurement of representative arterioles from each section in order to compute with any degree of accuracy the total reduction in the arteriolar bed in any one case.

In analyzing the data obtained from the study of these cases, I have divided them into three groups, the basis for this division being the estimated

*b**a*

FIG. 4a. Branches of the main pulmonary arteries. Moderate atherosclerosis may be noted; *b*, hypertrophy grade 3 of right ventricle. Note marked increase in the thickness of the ventricle which averaged 9 mm. in diameter.

severity classified as grade 2 or 2+; the second group included cases in which the degree of emphysema was graded 3 or 3+; and the final group consisted of only four cases, in all of which a most extreme degree of emphysema was present and was classified as grade 4.

### CORRELATION OF DATA AND COMMENT

Certain interesting correlations may be made from the data accumulated.

*Congestive Heart Failure in Emphysema.* Of the 32 cases death from cardiac failure with decompensation occurred in 14 cases or 44 per cent (table 1). In four additional cases death resulted from cardiorespiratory

TABLE 1

Comparison of Cardiac Findings and Occurrence of Congestive Failure in the Various Groups

Class	Grade of hypertrophy	Group 1* (20 cases)	Group 2 (8 cases)	Group 3 (4 cases)	Total (32 cases)	
		Number	Number	Number	Number	Per cent
Right ventricle	0	7	1	0		
	1 2 3	4 7 2 } 13	1 3 3 } 7	1 0 3 } 4	24	75
	Median grade	1	2	3		
Left ventricle	0	15	3	3		
	1 2 3	4 1 0 } 5	4 1 0 } 5	1 0 0 } 1	11	34
	Median grade	0	1	0		
Average heart weight, gm.		383	461	377	402	
Per cent increase above normal * †		28	41	35	32	
Congestive failure	Number	6	5	3	14	
	Per cent of group	30	63	75	44	

\* Group 1 consists of cases of emphysema, grade 2 or 2+. Group 2 of cases of emphysema, grade 3 or 3+ and group 3 of cases of emphysema grade 4.

† Based on calculation according to method of H. L. Smith.<sup>25</sup>

failure during severe attacks of asthma. The severity of the emphysema seemed to bear a direct relationship to the development of congestive heart failure, for there was a progressive increase in its occurrence in the more advanced cases of emphysema; for example, congestive heart failure occurred in 30 per cent of cases in group 1, in about 63 per cent of cases in group 2, and in 75 per cent of cases in group 3.

The development of cardiac decompensation secondary to pulmonary emphysema has been considered by numerous authors to be uncommon un-

monary infection.<sup>21, 22, 23</sup> 3. It may represent decrescent changes with age in a manner comparable with the changes in the systemic vessels. 4. There is a congenital predisposition or an inherent weakness of the vessels.<sup>24</sup> I shall not attempt to discuss the relative merits of these theories. It seems, however, from the findings just described that these changes when present in emphysema represent a secondary manifestation of an already present pulmonary hypertension which may best be explained by the compression and destruction of the capillary bed.

Steinberg has indicated that arteriosclerosis of the pulmonary vessels increases with advancing age in a manner similar to that in the systemic circulation. A close correlation might be expected, therefore, between the degree of pulmonary arteriosclerosis and the degree of sclerosis in the aorta and coronary vessels. When, however, the degree of aortic atherosclerosis (as graded on the basis of 1 to 4) is compared with the percentage reduction in arteriolar lumen, as high a median grade of aortic sclerosis is found

TABLE IV  
Comparison of Cardiac Findings and Pulmonary Arteriolar Measurements in Relation to Congestive Heart Failure

	Grade	Cases	
		Congestive heart failure	No congestive heart failure
Right ventricular hypertrophy	0	0	8
	1	0	6
	2	7	3
	3	7	1
Left ventricular hypertrophy	0	7	14
	1	7	2
	2	0	2
	3	0	
Reduction in pulmonary arteriolar measurements, per cent	0-9.9	3	8
	10-19.9	4	3
	20-29.9	4	4
	30-39.9	3	3
Total cases		14	18

in the group of cases without significant pulmonary narrowing (less than 10 per cent) as in that group in which the most marked narrowing of the pulmonary arterioles is present. There is also as high a median grade of coronary sclerosis in cases in which the reduction in the pulmonary arteriolar

finding of hypertrophy of the left ventricle in these cases represents a work hypertrophy and is explained most logically on the basis of hypertension in the systemic circulation which was not detected clinically.

*Pulmonary Arteriosclerosis.* On examination of the pulmonary arterial system it was found that in only six cases or 18.7 per cent were all the pulmonary arterial divisions normal. The frequency of arteriosclerosis in the pulmonary artery and its main tributaries did not seem to bear a direct relationship to the degree of emphysema. Gross atherosclerosis was noted in only one case in group 1 which included 20 cases; it was found in seven of the eight cases in group 2, but in only one of the four cases in group 3. On the other hand, the degree of arteriosclerotic involvement of the small muscular arteries increased with the severity of the emphysema. When the

TABLE II  
Summary of Pulmonary Arteriolar Measurements

Emphysema	Group 1* (20 cases)	Group 2 (8 cases)	Group 3 (4 cases)
Without arteriolar sclerosis	10 (50%)	0	1 (25%)
With arteriolar sclerosis	10 (50%)	8 (100%)	3 (75%)
Measurement of arterioles, per cent† Minimum	75	60	65
Maximum	107	86	103
Average	91	70	76

\* See footnote table 1.

† Measurements expressed in percentage of diameter of the normal lumen.

TABLE III  
Comparison of Degree of Pulmonary Arteriolar Narrowing with (1) Hypertrophy of the Right Ventricle, (2) Degree of Coronary Sclerosis, (3) Sclerosis of the Aorta

	Reduction in the average diameter of the arterioles, per cent			
	0-9.9	10-19.9	20-29.9	30-39.9
Total number of cases	11	7	8	6
Hypertrophy of right ventricle, median grade on basis of 0 to 4	1	2	2+	1+
Coronary sclerosis, median grade on basis of 0 to 4	1+	1	1+	1+
Aortic arteriosclerosis, median grade on basis of 0 to 4	2	2	2	2

reduction of the diameter of the arteriolar lumen was compared with the degree of emphysema, it was found that in 21 cases or 66 per cent of the entire group there was a reduction in the average arteriolar lumen amounting to 10 per cent or more; in 11 or 34 per cent of the cases there was no sig-



sion within the pulmonary circuit which probably is produced by obstruction in the capillary bed. Whereas it is reasonable to assume that when the degree of obstruction in the arteriolar system is great there is an augmentation of the pulmonary hypertension, it is doubtful that the amount of pulmonary arteriosclerosis seen in the usual case of emphysema produces alone a very marked obstruction to the pulmonary circulation.

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circulatory condition.<sup>18, 19</sup> The healthy heart, no doubt, can accommodate itself to obstruction in the pulmonary arterial system provided this obstruction is not too diffuse and the remainder of the vascular bed can dilate and transmit an increased flow of blood. In emphysema a demand exists for increased pulmonary circulation to compensate for the defective error in ventilation and the heart can be expected to meet this demand only as long as the vascular reserve is not exceeded.

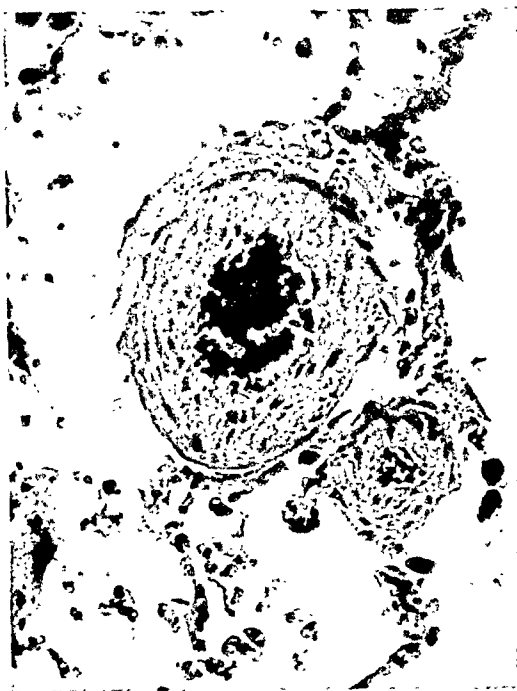


FIG. 3. Arteriole from same lung as shown in figure 2; marked hyperplasia of the medial layers may be noted. Diameter of the lumen approximately 60 per cent of normal ( $\times 200$ ).

In this series of cases an occasional case was seen in which the right ventricle had hypertrophied and failed and yet the arteriolar system seemed to present little or no obstruction. It must be assumed, therefore, that the vascular reserve of the lung may be exceeded as a result of capillary compression and destruction alone caused by the diffuse nature of the disease. In the majority of instances, however, secondary arteriosclerotic changes were found in the arterial and arteriolar systems which augmented the circulatory obstruction. If, in emphysema, the condition were not far enough advanced to provoke a real insufficiency in ventilation, the heart may compensate for the obstructive phenomenon, but when both factors, ventilation and circulation, are disturbed sufficiently, the heart sooner or later must fail (figures 2, 3, 4 and 5).

In view of the almost constant relationship between the degree of emphysema and the amount of obliteration of the arteriolar bed, and in view of the consistent increase in hypertrophy of the right ventricle in association

# THE DIAGNOSTIC VALUE OF REGRESSION OF SECONDARY SEXUAL CHARACTERISTICS IN CASES OF HEMOCHROMATOSIS \*

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CASE reports of hemochromatosis associated with regression of the secondary sexual characteristics have appeared in the literature sporadically.<sup>1, 2, 3, 4</sup> It is not generally appreciated, however, that these findings may appear relatively early in the course of the disease and, therefore, give a clue to the diagnosis before bronzing of the skin, enlargement of the liver, and diabetes become diagnostically manifest. The two cases herein reported are illustrative. The first case was studied before we were aware of the fact that signs of hypogonadism or anterior pituitary insufficiency occurred in conjunction with hemochromatosis. As there was comparatively little pigmentation present, the making of the diagnosis was difficult in the first case. In fact, the diagnosis was made somewhat accidentally and the possibility of hemochromatosis was not very seriously entertained before the results of biopsy of the skin were reported. In the second case, however, largely because of our experience with the first case, the possibility of hemochromatosis was immediately entertained even though there was very little pigmentation present and the urine contained no sugar.

## CASE REPORTS

*Case 1.* A man, aged 47 years, a railway brakeman who was not addicted to the use of alcohol, registered at the clinic in November 1929. Six months previously, symptoms of diabetes mellitus had appeared, and two months later sugar was found in the urine. The blood pressure was 120 mm. of mercury systolic and 84 mm. diastolic. The edge of the liver was palpable 3 cm. below the right costal margin anteriorly, but otherwise his examination disclosed nothing of consequence except a partial *nasal* hemianopsia of the right eye. As the result of treatment with insulin, his health improved so that for the next seven years he was able to work at his occupation.

In January 1936, the right hand became infected. Shortly thereafter his abdomen began to enlarge because of ascites. Periodic removal of the fluid by paracentesis became necessary. On April 6, 1936, the patient again reported at the clinic for examination. It was found that he was 5 feet 10 inches (175 cm.) in height and weighed 123 pounds (55.9 kg.). He was decidedly emaciated. The skin was dry and sallow. There was a suggestion of generalized pigmentation and there was considerable pigmentation over the shin bones, but the pigmentation was not as noticeable as the accompanying photograph (figures 1 and 2) would indicate.‡ The beard

\* Received for publication May 9, 1940.

† Now residing in Chicago, Illinois.

‡ Possibly the pigmentation would have been more noticeable had he not been occupying a room with an individual who was intensely pigmented and who was suspected of having, but did not have, hemochromatosis.

with increase of severity of emphysema, there should be a direct correlation between the degree of arteriolar obliteration and the amount of hypertrophy of the right ventricle. This assumption is not true, for when the hypertrophy of the right ventricle in cases of minimal pulmonary arteriolar obliteration (10 per cent or less) is compared with that in cases of moderate to advanced pulmonary arteriolar obliteration (20 per cent or more) no increase is found in the frequency or degree of right ventricular hypertrophy in the latter cases (table 3). The presence of pulmonary arteriolar narrowing in emphysema, therefore, does not seem to affect the right ventricle as



FIG. 5. Pulmonary arteriole showing irregular intimal and medial hyperplasia. Measurements of arterioles in this case revealed the average diameter of the lumen to be 73 per cent of normal. Section from same case as figure 4.

much as one would expect. The factors producing pulmonary hypertension in emphysema must exist then, whether or not arteriolar changes are associated. It is reasonable to assume that when arteriolar narrowing is advanced the pulmonary hypertension must be augmented, but it is doubtful whether the pulmonary arteriosclerosis seen in emphysema represents a primary change.

The question of the etiology of pulmonary arteriolar sclerosis is controversial. Various theories have been suggested. These are as follows: 1. The sclerotic change is a secondary manifestation of an already present hypertension in the pulmonary circuit and thus is a manifestation of the increased stress and strain on the pulmonary vessels.<sup>11, 20</sup> 2. The development of pulmonary arteriosclerosis is a secondary manifestation of pul-

seemed to be normal but the cutaneous hair elsewhere was very scanty. The axillary and pubic hair was diminished and the latter was feminine in its distribution. Free fluid was demonstrated in the abdomen. The liver was enlarged and readily palpable about 8 cm. below the costal margin, but the spleen could not be felt. The edge of the liver was thickened and rounded. One hemorrhage was found in the retina of



FIG. 2. Note the scanty axillary hair, and the absence of hair on the chest and around the nipples.

the right eye. The retinal arteries were slightly narrowed and there was some pallor of the right optic nerve head. The nasal hemianopsia was again noted. The blood pressure, in millimeters of mercury, varied from 120 to 140 systolic and from 70 to 80 diastolic.

In brief, the appearance of the patient was not greatly unlike that which occurs in cases of Simmonds' cachexia, except for the fact that ascites and hepatomegalia were present.

Although the laboratory studies (table 1) resulted in diagnoses of diabetes mellitus, probable cirrhosis of the liver, nephritis (type undetermined) and coronary sclerosis, we nevertheless had the impression that there was an additional pathologic factor present. Mainly because the liver was enlarged, a biopsy of the skin was performed. Somewhat to our surprise the skin showed the changes unquestionably diagnostic of hemochromatosis.

lumen is minimal as in those in which pulmonary arteriolar sclerosis is most marked (table 3). These findings then indicate that pulmonary arteriolar sclerosis in emphysema is not representative of the degree of degenerative arterial changes in the systemic or coronary circulation. This lends further support to the opinion that these changes in the pulmonary arterioles associated with emphysema are secondary manifestations of pulmonary hypertension.

Another interesting correlation can be made if the cases of emphysema in which congestive heart failure occurred are analyzed further (table 4). Mention already has been made of the fact that the incidence of congestive failure increased with the intensity of emphysema. It may now be pointed out that congestive heart failure in these cases represented primarily a failure of the right ventricle, for in all these cases there was moderate to marked, grade 2 to 3, hypertrophy of the right ventricle whereas the left ventricle was not enlarged in seven instances and was enlarged minimally or grade 1 in the remaining seven cases.

As mentioned in the foregoing, the degree of pulmonary arteriolar obliteration itself does not seem to influence greatly the amount of right ventricular enlargement, yet it is of interest to note that in the cases of congestive failure there were only three out of the 14 cases in which there was no appreciable reduction in the arteriolar lumen, whereas in eight of the 18 cases in which congestive failure did not occur there was no appreciable arteriolar obliteration. I feel that although in emphysema these arteriolar changes may not play a predominant rôle in the production of hypertension within the pulmonary circulation, they must aid to some extent in bringing about the ultimate failure of the heart.

#### SUMMARY

An anatomic study was made of the heart and pulmonary arterial tree in 32 cases of essential emphysema. It was found that emphysema produced enlargement of the right ventricle in 75 per cent and resultant cardiac failure with decompensation in 44 per cent of the entire group. The severity of emphysema seemed to be closely correlated with the incidence of congestive heart failure as well as to the frequency and extent of right ventricular enlargement. Arteriosclerosis of the pulmonary arterial tree was noted to some degree in 80 per cent of the cases. Arteriosclerotic changes were noted most frequently in the arterioles, and narrowing of the arteriolar bed was found in 66 per cent of the total cases studied. The degree of obliteration of the arteriolar bed seemed to be influenced by the severity of emphysema, yet there was no direct correlation between the degree of arteriolar sclerosis and the degree of right ventricular enlargement, nor any relationship between the extent of these pulmonary arteriolar changes and the extent of arteriosclerotic changes in the coronary arteries or the aorta. It was concluded, therefore, that the arteriosclerotic changes of the pulmonary vessels in emphysema represent secondary manifestations of an existent hyperten-

Physical examination revealed a slender, poorly developed man who was 5 feet 7 inches (167.5 cm.) in height and weighed 131 pounds (59.5 kg.). The hips were broad. His appearance was not unlike that of patients suffering from chromophobe tumor of the anterior pituitary body, and this possibility was immediately entertained. The skin, except for the exposed surfaces, was fine, somewhat waxy in color, and largely devoid of hair. The beard was sparse, the axillary hair absent, and the scanty pubic hair was distributed in typical feminine fashion. That portion of the skin which had been exposed to the light was slightly pigmented and there was some pigmentation of the creases of the palms, but there was no pigmentation of the buccal mucosa, lips, or gums. The liver was diffusely enlarged, firm, and easily palpable 4 cm. below the right costal margin, anteriorly. The spleen could not be felt. Both testes were small and atrophic. The blood pressure, in millimeters of mercury, was 106 systolic and 70 diastolic. Roentgenologic examination of the head, thorax, and spine disclosed no abnormal findings. The sella turcica was not enlarged. Erythrocytes numbered 4,750,000, leukocytes 4,800 per cubic millimeter. The content of the hemoglobin in the blood was 14.0 gm. per 100 c.c. The flocculation test for syphilis was negative. No retention of dye occurred with the bromsulfalein test for liver function. The serum bilirubin was found to be 1.3 mg. per 100 c.c. and the van den Bergh reaction was indirect. The basal metabolic rate was — 3 per cent. A glucose tolerance test yielded the results shown in table 2.

TABLE II  
Results of Glucose Tolerance Test

Time, hrs.	Blood sugar, mg. per 100 c.c.	Sugar in urine
* 0 (fasting)	112	0
$\frac{1}{2}$	233	0
2	147	0
3	90	0

\* One gram of glucose per kilogram of body weight was given.

Because of the enlarged liver and the signs of hypopituitarism and hypogonadism, a tentative diagnosis of hemochromatosis was made. The diagnosis was established by a biopsy of the skin which disclosed the typical deposits of hemosiderin around the sweat glands.

A diet containing liberal amounts of carbohydrate and treatment with testosterone propionate were advised. Three months later the patient suddenly died at home.

#### COMMENT

Hemochromatosis is a rare disease. It occurs chiefly but not exclusively among men. The etiology has never been determined. Possibly because of an inborn intracellular metabolic disturbance,\* large amounts of hemosiderin, a pigment containing iron, become lodged within the cells of most of the organs of the body with the possible exception of the nervous system. The cells become so stuffed with pigment that degeneration or death of the

\* For a detailed discussion of the entire subject the reader is referred to the very excellent monograph by Sheldon.<sup>6</sup>

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possibly the adrenal glands and testes. The pigmentation of the skin results from the increase of melanin and the deposition of hemosiderin and varies according to the relative amount of each present.

Fortunately, for clinical purposes, both hypogonadism and hypofunction of the anterior lobe of the pituitary body result in easily recognizable physical stigmas. In both of these conditions there occur a fairly characteristic pallor, loss of beard and of pubic and axillary hair, infantile genitalia and often distinctive changes in the habitus. It makes very little difference, for the time being, whether we regard these changes as evidence of hypogonadism secondary to deposits of pigments in the testes themselves or hypogonadism that in turn is the result of hypopituitarism. If any appreciable amount of diabetes coexists, as it did in case 1, current endocrinologic theory would favor the view that the testicular insufficiency is the direct result of the pathologic changes that occur in the testes.

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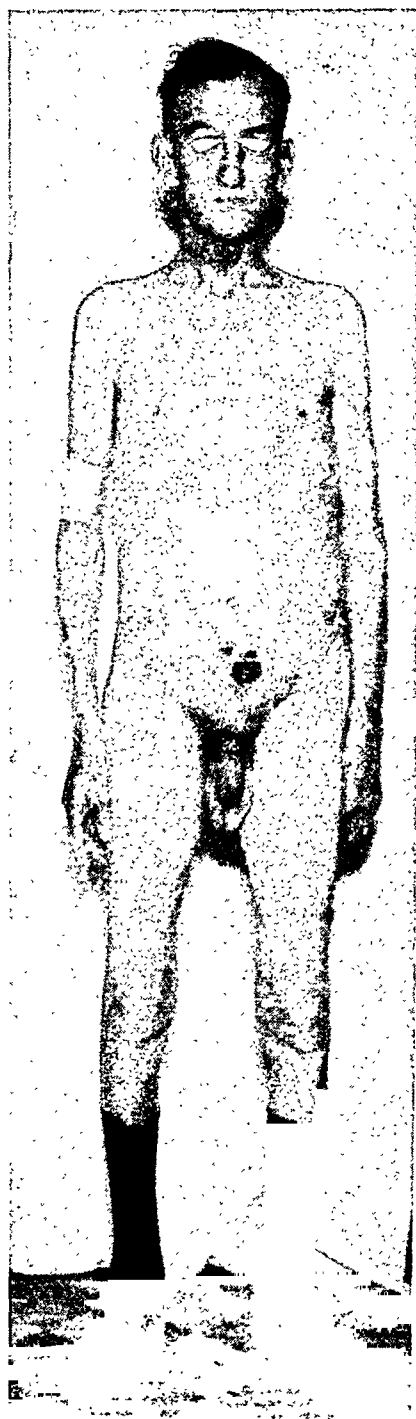


FIG. 1. Appearance of patient on admission to the hospital. Note the scanty pubic hair. The face, hands, and neck appear more pigmented than they actually were. Compare with figure 2.

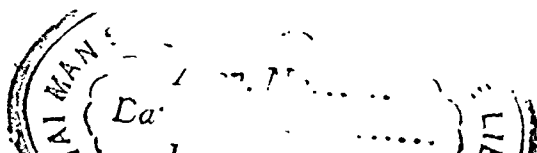


TABLE I

No.	Sex	Age	Height	Weight	Weight Loss	Duration	B.P.	Pulse	Temp.	Precipitating or psychic factor	Menses and duration of amenorrhea	
1.	F	24	67"	70 lb.	118 lb.	4 yrs.	115/80	80	98.2	Reducing diet	2 yrs.	14
2.	F	24	61"	52 lb.	62 lb.	5 yrs.	98/70	76	96.0	Appendectomy	1 period per yr. for past 6 yrs.	16
3.	F	34	60"	59 lb.	59 lb.	10 yrs.	100/84	72	98.4	Hysterectomy (ovaries not removed)	3 periods in 10 yrs.	14
4.	F	17	64"	89 lb.	50 lb.	12 mos.	92/58	68	95.0	Quinsy and tonsillitis	1 year	11
5.	F	20	61"	82 lb.	40 lb.	3 yrs.	105/80	58	99.0	Over-industry in college	3 yrs.	12
6.	F	36	61½"	94 lb.	40 lb.	6 mos.	122/70	64	98.0	Religious ?	Surgical menopause	
7.	F	25	61"	75 lb.	40 lb.	12 mos.	86/70	44	98.0	Reducing diet	10 months	12
8.	F	18	63"	86 lb.	40 lb.	16 mos.	106/54	58	96.4	Over-industry in school	2 yrs.	14
9.	F	16	61"	92 lb.	40 lb.	12 mos.	80/50	42	97.0	Appendectomy	4 months	12
10.	F	22	65½"	82 lb.	38 lb.	2 yrs.	94/60	60	98.0	Over-work away from home	18 months	14
11.	F	19	67"	108 lb.	35 lb.	6 mos.	110/68	84	96.8	Unable to elicit	3 months	14
12.	F	16	63"	78 lb.	32 lb.	12 mos.	90/45	60	96.0	Restricted diet to simulate a girl friend	10 months	13
13.	M	27	65"	85 lb.	32 lb.	14 mos.	80/60	68	97.6	"Afraid to eat" because of G-I dis- tress	Male patient	
14.	F	20	62"	69 lb.	31 lb.	10 mos.	120/80	70	98.0	Hysterical attacks	2½ yrs.	15
15.	F	18	63½"	50 lb. lowest 59 lb.	30 lb.	8 yrs.	66/7	62	97.2	Globus hystericus	Primary amenorrhea	
16.	F	26	64"	93 lb.	27 lb.	2 yrs.	106/80	64	98.0	Not elicited	12 mos.	14
17.	F	19	61"	79 lb.	26 lb.	15 mos.	90/50	43	98.0	Over-industry in school precipitated with commencement	Scanty	14

TABLE I  
Special and Laboratory Studies

Urine	Blood
Specific gravity, 1.010-1.015	Hemoglobin, 11.1 gm.
Albumin, grade 3	Erythrocytes, 3,580,000 to 4,380,000
Pus, grade 1 to 3	Leukocytes, 6,900
Erythrocytes, grade 1 to 3	Differential count:
Sugar, 0 to 21 gm.	Lymphocytes, 13.0 per cent
Acetone, occasionally present	Monocytes, 3.5 per cent
Urobilin, 0	Neutrophiles, 82.5 per cent
Urobilinogen, 0	Basophiles, 1.0 per cent
Hemosiderin, 0	Slight poikilocytosis and anisocytosis
Culture: <i>Escherichia coli</i> present	There was no evidence of macrocytosis
	Flocculation test for syphilis negative
Blood chemistry (in mg. per 100 c.c. unless otherwise specified)	
Sugar, 112 to 345	Sulfates, 7.0 to 7.8
Carbon dioxide combining power, 46.6 vols. per cent	Sodium, 339 to 342
Chlorides, 511 to 635 (as NaCl)	Potassium, 25.3
Cholesterol, 264	Serum protein, 6.8 gm.
Calcium, 9.2	Albumin-globulin ratio, 1.06:1
Phosphate, 4.8	Serum bilirubin, 1.0
Phosphatase, 2.3 units	Van den Bergh reaction, indirect
	Urea, 39 to 76

#### Miscellaneous examinations

Roentgenograms of the head, sella turcica, and thorax: negative  
 Roentgenograms of the right leg: marked calcification of the arteries; dense osteitis of the anterior and lateral aspects of the midportion of the tibia  
 Intravenous urogram: renal function too poor to outline kidneys  
 Electrocardiogram: sinus tachycardia, iso-electric T-waves in derivation I, diphasic T-waves in derivations II and III  
 Paunz test for amyloid disease: negative  
 Liver function test (bromsulfalein method): no retention of dye  
 Urea clearance: 37.8 c.c., volume 180 c.c.  
 Sulfate clearance: 29.6  
 Examination of ascitic fluid—Pon's test for hemosiderin: negative  
 Basal metabolic rate: 0 to —5 per cent

With treatment, the condition of the patient improved. The diabetes presented no difficulties and was readily controlled by regular insulin (60 to 75 units) and by a diet containing 300 gm. of carbohydrate, 79 gm. of protein, and 100 gm. of fat. Shortly after the patient's admission to the hospital 4,500 c.c. of clear fluid were removed from the abdomen by paracentesis. Later, satisfactory diuresis could be maintained by administering orally 12 gm. of potassium nitrate or potassium chloride daily. The administration of either of these salts obviated tapping the abdomen and reduced the concentration of the blood urea. The patient was dismissed in relatively good condition. Three months later he died at home. As necropsy was not performed, we never learned the nature of the renal lesions. Renal insufficiency is an unusual complication of hemochromatosis, possibly because hemosiderin is deposited in the renal cells to a limited extent as compared with other parenchymatous organs.\* Chronic pyelonephritis might easily have been the etiologic factor.

Case 2. A white man, aged 40 years, a University professor, came to the clinic August 2, 1939, because of fatigue and an ache low in the back. He had been married eight years and for the last six years he had been impotent. When coitus was possible there was no ejaculation. Previously, his health had been exceptionally good. He was not addicted to alcohol. He was unaware of any change in the color of his skin except what he could attribute to exposure to the sun.

\* The case reported by Hurxthal is an exception to the rule.<sup>5</sup>

TABLE I (continued)

No.	Sex	Age	Height	Weight	Weight Loss	Duration	B.P.	Pulse	Temp.	[Precipitating or psychic factor	Menses and duration of amenorrhea	Menarche Age
18.	F	25	59"	71 lb.	24 lb.	3 yrs.	90/60	76	98.0	Dysphagia (no organic basis for this)	3 yrs.	12 yrs.
19.	F	25	66"	96 lb.	24 lb.	2 yrs.	100/80	56	98.0	Marriage ?	Irregular and scanty	15 yrs.
20.	F	13	57"	63 lb.	22 lb.	6 wks.	90/50	68	96.0	Reducing weight (acute starvation)	2 mos.	12 yrs.
21.	F	30	60½"	88 lb.	22 lb.	12 mos.	98/60	68	96.8	Not elicited	Irregular 2 yrs.	14 yrs.
22.	F	29	61½"	80 lb.	22 lb.	2 mos.	110/70	88	98.6	Disappointment in love affair—definite	Scanty—regular	13 yrs.
23.	F	21	65½"	88 lb.	20 lb.	10 mos.	95/60	56	98.0	Spontaneous abortion	10 mos.	14 yrs.
24.	F	17	62"	82 lb.	20 lb.	2 yrs.	75/60	64	94.2	Not elicited	12 mos.	15 yrs.
25.	F	27	65"	87 lb.	20 lb.	12 mos.	130/90	80	98.6	"Psychoneurotic type"	Surgical menopause at 18 yrs.	13 yrs.
26.	F	18	65"	83 lb.	20 lb.	2 yrs.	115/60	80	96.0	Incapability in high-school	Irregular and scanty	13 yrs.
27.	F	17	61¾"	90½ lb.	15 lb.	2 yrs.	100/60	44	97.0	Over-industry in school	17 mos.	14 yrs.

little to the clinical picture. In some cases the disturbed endocrine functions are especially interesting. Our findings in this respect will be discussed later. It frequently occurs, as it did in several of our own cases, that the condition is at first mistaken for Simmonds' disease and is separated from it with difficulty and often only after observation for some time.

### ETIOLOGY

It is generally accepted that the background for this condition is a "morbid mental state," and Ryle<sup>11</sup> has pointed out the importance of searching for multiple contributing factors as to psychogenic cause. He states that "of all the diseases in which the adverse interactions of the mind and body play a part, anorexia nervosa is one of the most dramatic and significant. A psychic trauma or a foolish habit, or some combination of the two, results in a loss of appetite and a suppression of the menses. Starvation follows and with the starvation an aggravation of the anorexia. Faced with these symptoms and increased emaciation, domestic anxiety, and sometimes medical indecision still further complicating the situation, a young

cell, sometimes from rupture, occurs. The secreting cells of the glands of internal and external secretion, their connective tissue stroma, striated and cardiac muscle, the reticulo-endothelial system, the alveolar epithelium of the lungs, the cartilage and synovium of joints, and occasionally the walls of the blood vessels are the favorite sites for the pigment. In the adrenal glands a heavy deposit of hemosiderin may be found in the zona glomerulosa, but the remainder of the cortex and the medulla are unaffected. A marked deposit of pigment is found in the anterior pituitary body, particularly, according to Sheldon,<sup>6</sup> in the basophilic cells. The pars nervosa, like the adrenal medulla, escapes involvement. In the testes, the cells of the germinal epithelium become atrophic. There is little information regarding the condition of the interstitial cells. Curiously, to a large extent, the cells of the kidneys escape involvement. The same remark applies to smooth muscle.

Hemofuchsin, an iron-free pigment, is also deposited in some cells. On the whole, it is found most abundantly in those organs and cells that are least affected by hemosiderin, for example in smooth muscle. However, it also occurs in connective tissue and in the epithelial cells of the glandular organs. Histologically, the cells of the thyroid and parathyroid glands are found to be the sites of extensive pigmentation. In the skin there is not only a deposition of hemosiderin, especially in and around the sweat glands, but there is in addition a marked increase in melanin, the normal skin pigment, especially in the deep layers of the corium.

In addition to the histologic changes just mentioned, an extensive sclerosing process occurs in the thyroid gland, liver, pancreas, and spleen. This sclerosis is nonspecific in character and in the last three organs enumerated, it resembles the fibrosis that occurs in ordinary cases of cirrhosis of the liver.

From what has been said, it is evident that hemochromatosis affects the histologic structure of most of the cells of the body. What is truly remarkable is that the function of so many organs apparently is unaffected. For example, in our experience, even though the liver is extensively involved even to the point of producing ascites, hepatic function as measured by the elimination of bromsulfalein usually is not disturbed (case 1). The thyroid gland likewise apparently tolerates both the pigmentation and the fibrosis very well. In other words, myxedema\* and parathyroid tetany as the result of hemochromatosis occur exceedingly rarely, if at all. To our knowledge there is only one case of hemochromatosis on record in which clinical evidence of adrenal cortical insufficiency has been demonstrated.<sup>5</sup>

The clinical features of the disease, namely cirrhosis of the liver, diabetes, pigmentation and sexual hypofunction, therefore, are readily explicable by the gross and histopathologic findings, namely sclerosis or pigmentation or both, of the liver, pancreas, anterior lobe of the pituitary, and

\* In one of the cases studied by Butt and Wilder<sup>7</sup> at the clinic, the basal metabolic rate was — 19 per cent but the clinical signs were not sufficiently definite to warrant a diagnosis of myxedema.

## SYMPTOMATOLOGY

A. *Anorexia*. The anorexia in these cases may be described as a loss of appetite and hunger amounting to a disgust for food. Everyone readily admits a large psychic element in nutrition. The situation is well stated by Keeton <sup>24</sup>: "the vegetative mechanism is constantly subjected to reflexes originating in the mental fields, if these are pleasurable there is a facilitation of digestion, if they are not there is an inhibition." A disturbing bit of news is received and the individual loses his appetite, if the adjustment is difficult he may become nauseated and vomit. One has only to look at the nervous worried patients who are suffering from anxiety neuroses to realize the great blockade that the mind offers in these patients to maintenance of a normal nutritional state."

Surmont <sup>10</sup> states that he found achlorhydria present in the type of person who is subject to anorexia nervosa. Berkman <sup>18</sup> reported a tendency to hypoacidity in his series of cases. There were 12 cases in our series that had Ewald test meals; achlorhydria was present in only one.

Our results were as follows:

## Number of cases:

1  
3  
3  
5

## Degree of Free Acid:

No free acid  
Below 20 degrees  
Between 20 and 40 degrees  
Above 40 degrees

Achlorhydria, therefore, is not a factor of importance in causing the anorexia in these cases.

B. *Loss of Weight, Emaciation, and Effects of Weight Loss*. One of the basic abnormalities in this disease is the failure of the patient to accept an adequate diet. As soon as there is insufficient food for body processes the tissues are utilized, and this produces weight loss. To protect these tissues when the intake is lowered the basal metabolism becomes depressed. In starvation, the carbohydrate stored as glycogen and the so-called "deposit protein" are oxidized first, later the body fat is drawn upon, and finally the body protein. The tissues of greatest physiologic importance are spared as long as possible. When the most vital organs are sapped, death results.

One of the most instructive accounts of the effect of starvation on oxygen metabolism is that given by Benedict <sup>26</sup> in his studies on a group of students:

"A group of 12 athletic young men, who were on diets of 3200 and 3600 net calories per day, were placed on a diet of 1400 calories for three weeks without changing their mental or physical activities. After the average weight had fallen 12 per cent below its original level, it was found that they were able to maintain this weight on a diet of 1950 calories, a little more than half of the amount originally required. Meanwhile the heat production during sleep had fallen to about three-fourths of its original value,

## ANOREXIA NERVOSA \*

By E. PERRY McCULLAGH, M.D., F.A.C.P., and WALTER R. TUPPER, M.D.,  
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IN 1868 Sir William Gull,<sup>1</sup> in an address at Oxford, first referred to a "peculiar form of disease occurring mostly in young women, and characterized by extreme emaciation." He presented a paper on the subject in 1874, in which he stated that the origin of the disease is "to be sought in the disturbance of the mind and a prolonged insufficiency of food and nothing more." Other writers described the condition,<sup>2, 3</sup> but Gull deserves credit for the name and the concept of the condition which is accepted at present.

There are several papers by the English writers<sup>4, 5, 6, 7, 8, 9, 10</sup> which deal with case presentations, and a very complete account is given by John A. Ryle.<sup>11</sup> Other English writers have described possible mechanisms involved in the production of the syndrome.<sup>12, 13, 14</sup>

The French have written vivid descriptions and have discussed etiologic factors.<sup>15, 16, 17,</sup>

In this country there has been comparatively little material presented concerning this entity until the recent publications<sup>18, 19, 20, 21, 22, 23</sup> which report cases and consider differential diagnosis.

This paper is based on the study of 27 cases of anorexia nervosa.

### CLINICAL PICTURE

The most striking single feature of anorexia nervosa is the extreme degree of emaciation present. It has been stated that the emaciation with marked retraction of the abdomen, sunken eyes and dilated pupils is comparable only to that of cancer of the esophagus. Important clinical features include: an abnormal psychic attitude, anorexia, amenorrhea or irregular scanty menses, weakness, and many varied gastrointestinal symptoms. The weight loss varies in accordance with the length of the illness and the acuteness of the anorexia. It is impressive that the patient may complain of little, and may even desire not to be treated, but may be brought in by concerned parents or relatives. Some of the patients complain of dryness of the skin and hair, brittleness of the nails, loss of libido sexualis, intolerance to cold, and appearance of premature aging.

The physical and laboratory findings include: lowered blood pressure, slow pulse, subnormal temperature, lowered basal metabolism, and sometimes alterations in the glucose tolerance curve. Roentgen examinations of the skull, chest, gastrointestinal and genitourinary tracts, visual field examinations, and the information gained by various special examinations add

\* Received for publication November 27, 1939.



at the beginning of the experiment. They lacked energy, they felt cold more keenly, and there was a marked diminution in sex expression coincident with reduced diet."

The above experiment demonstrates clearly the major effects of starvation, and emphasizes the fact that strength may be well maintained during

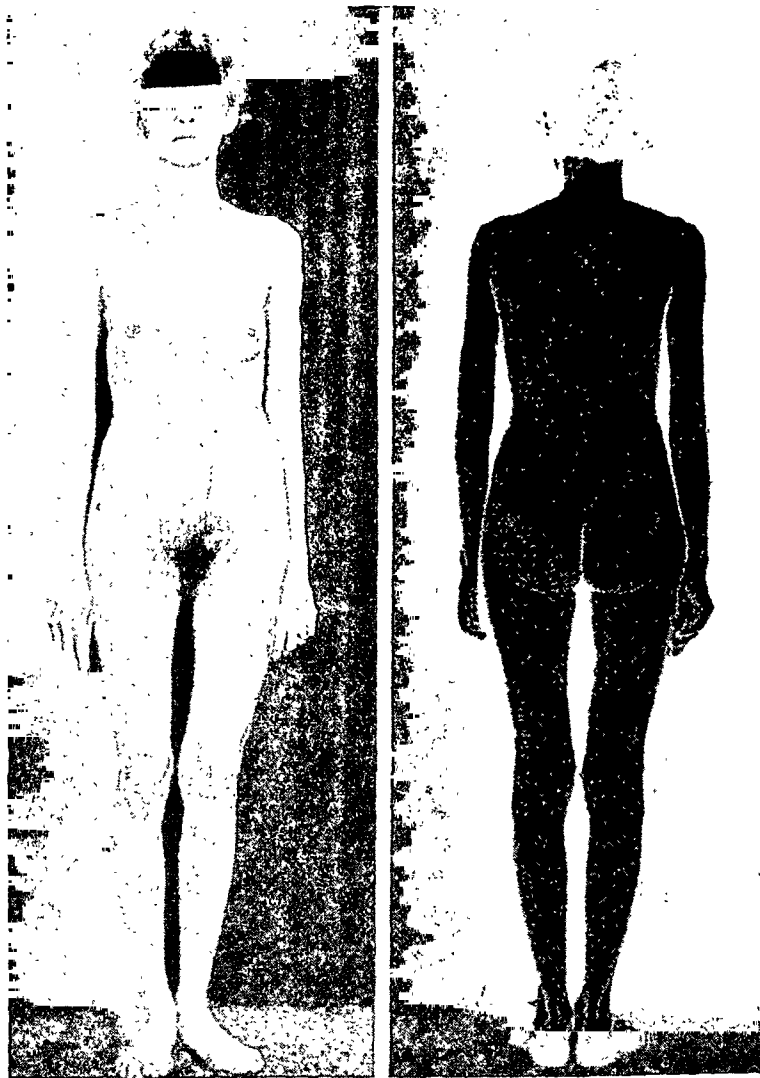


FIG. 2. *Case 2.* Five years later. Age 29 years, height 61 inches, weight 83 pounds. Note: The incisional scars present at this time resulted from an operation to "suspend the uterus" and two exploratory laparotomies for "abdominal adhesions."

considerable weight loss. Further effects of marked weight loss are marked weakness and inability to walk; and Keeton<sup>24</sup> has seen incontinence of urine and feces, suggesting the possibility of cord lesions. Such cases have been shown to be secondary to malnutrition, since the signs disappeared when food was administered.

Among our cases, two were fatal (cases 6 and 15); and in both in-

TABLE I

Bio-Assays		B.M.R.	Glucose tolerance	Weight gain	Period of follow-up	Response	Remarks
Friedman	Urinary estrogens and androgens						
Positive	10-20 R.U.	-32%	94-125-128-111-90-97	60 lbs.	2 yrs.	Good	Under intensive endocrine therapy and repeated treatment in hospital this patient's weight dropped to 70 lbs. A remarkable recovery followed forced tube feedings after all endocrine therapy was discontinued.
Negative	Not done	-19%	95-179-154-160-102-77	31 lbs.	4 yrs.	Fair	There is a history of repeated hospitalizations and operations, and a psychiatric examination showed "a deep-seated neurologic defect."
Positive	20-30 R.U.	-11%	94-208-224-319-313-178	14 lbs.	6 mos.	Fair	This patient made excellent response while hospitalized (gain of 14 lbs. in 15 days) but since returning home has not improved. Diet not continued.
Positive	Less than 4 R.U.*	-42%	86-86-117-187-190-113	68 lbs.	5 yrs.	Good	Very little response to intensive endocrine therapy for a period of 3 years, then after stopping all therapy made a spontaneous recovery.
Measurable prolan	Less than 4 R.U.*	-24%	65-109-165-117-61-60	48 lbs.	2 yrs.	Good	Given endocrine therapy while in hospital for a short time; after returning home and discontinuing her college education she recovered.
Not done	Not done	-15%	73-172-187-158-95-89	None	—	Died	This patient desired to return home where all attempts failed, although tube feedings were not tried; partial necropsy revealed no cause of death. The pituitary was not examined.
Negative	Less than 4 R.U.*	-38%	84-113-113-109-98-80	14 lbs.	4 yrs.	Poor	Still maintains a highly neurotic temperament, often telephoning her physician to see if she should eat or not.
Not done	Not done	Not done	62-2½ hrs. p. p.	46 lbs. (in 9 mos.)	8 yrs.	Good	After reassurance this patient returned to her home and gained 46 lbs. in 9 months.
Not done	Less than 10 R.U.	-43%	88-3 hrs. p. p.	?	2 yrs.	Good	Obstinate constipation resulted in suggesting an operation for adhesions. Exploratory laparotomy only was followed by complete recovery.
Measurable prolan	Less than 10 R.U.	-21%	4/27/38: 91-114-102-64-110-49 12/28/38: 97-152-136-126-51-79	40 lbs. (in 9 mos.)	1 yr.	Good	Thyroid was the only therapy aside from diet and the patient had taken only a total of 5½ grains when her first menstrual period returned.
Negative	Less than 10 R.U.	-26%	73-120-178-160-160-127	None	4 mos.	Poor	A follow-up letter from this patient reveals that her mental attitude has improved but she has little appetite and no weight gain as yet.
Measurable prolan	10-20 R.U.	-24%	78-84-128-110-103-81	16 lbs.	2 yrs.	Fair	Has not followed diet or rest as suggested, but mental attitude has improved. The death of this patient's mother during this period may be a factor in the slow progress.
Positive	Androgens 12 U.	-40%	78-87-103-89-90	7 lbs.	2 yrs.	Poor	No response to repeated reassurance and encouragement; this patient lives from charity funds and seems very well contented to remain ill.
Not done	Not done	-13%	9/26/30: 74-134-180-153-138 1/10/39: 84-230-236-70-85-45	26 lbs. (in 6 mos.)	8 yrs.	Good	This case made a spontaneous recovery after she became interested in music.
Negative	Not done	-25%	56-104-111-105-84-70	None	—	Died	Fatal. This patient had intensive and energetic endocrine therapy for several months without improvement; tube feedings were started late in the course of her illness at home, but she just "faded away." Necropsy not done.
Negative	30-40 R.U.	-23%	87-125-172-170-161-62	None	2 yrs.	Poor	There was an adequate trial on endocrine therapy without response. Attempt at recent follow-up has been unsuccessful.
Negative	Not done	-20%	73—fasting	20 lbs.	2 mos.	Good	Good prompt response.

cases had irregular and scanty periods; three cases had had operative interference previously; and in one case there were irregular and mildly profuse menstrual periods. The menarche was at 13 to 14 years in the majority of cases, the extremes being 11 to 16 years.



FIG. 4. Case 10. Age 22 years, height  $65\frac{1}{2}$  inches, weight 82 pounds, weight loss 38 pounds in 2 years.

With regard to the etiology of the amenorrhea, it appears that the starvation is the chief factor in most cases, as the amenorrhea usually follows considerable weight loss. The nervous or psychic factor, however, is apparently the major factor in some since the amenorrhea may precede weight loss as occurred in two of our cases. It appears to us that both factors are of importance. Whether the amenorrhea is psychic or nutritional, the mechanism must involve ovarian activity. Whether this is primary or pituitary in origin is not certain. Some of the hormonal studies appear to bear definitely on this point.

TABLE I (continued)

Bio-Assays		B.M.R.	Glucose tolerance	Weight gain	Period of follow-up	Response	Remarks
Friedman	Urinary estrogens and androgens						
Positive	Less than 4 R.U.	-21%	106-168-176-147-87-73	73 lbs. (in 3 yrs.)	5 yrs.	Good	This case had intensive endocrine therapy for a period of two years under observation here without any response; then after becoming interested in "Christian Science" made a complete recovery. At this time we have the patient on a mild reducing diet.
Negative	Not done	-13%	92-3 hrs. p. p.	40 lbs.	2 yrs.	Good	No endocrine therapy was given in this instance, and the recovery has been satisfactory.
Not done	Not done	-38%	107-fasting	40 lbs. (in 10 mos.)	6 yrs.	Good	Firm handling at home and dietary therapy alone accounted for this excellent response.
Not done	Not done	- 8%	12/30/35: 94-176-187-118-80-45 1/16/36: 89-95-76-74-82-74	21 lbs.	7 yrs.	Fair	Following a trial on pituitary extract, antuitrin-S and insulin, dietary management alone has shown a fair response.
Not done	Not done	-20%	105-fasting	15 lbs.	2 yrs.	Poor	This is a very unstable nervous type of individual, and there has been a poor response to repeated encouragement and reassurance.
Positive	Less than 10 R.U.	-30%	8/25/37: 60-99-114-73-99-62 5/2/38: 73-98-107-104-51-59	20 lbs.	2 yrs.	Fair	Ovarian therapy with A. P. L. for a three-month period with cooperation in the diet accounted for this fair response.
Not done	Not done	Not done	Not done	6 lbs.	5 mos.	Poor	No response to theelin, whole pit. extract, and antuitrin-S therapy.
Negative	Not done	- 2%	82-4 hrs. p. p.	25 lbs.	2 yrs.	Fair	There is a gradual improvement in this case.
Not done	Not done	Not done	80-2½ hrs. p. p.	13 lbs.	4 yrs.	Poor	This patient still has periodic episodes of "getting nervous and having vomiting spells and loss of appetite."
Positive	10-20 R.U.	-27%	83-173-193-145-69-74	3½ lbs. (in 10 days)	—	Good	During 17 months of amenorrhea, various endocrine preparations were given without benefit. Under observation short time with increase in weight. No menses as yet.

\* Estrogen assays done by the method of Kurzrok.<sup>37</sup> The others were done by Cuyler's method.<sup>31</sup>

woman, recently healthy and happy begins to cause alarm and to look 'like a victim of a famine privation.'"

One or more factors may be important in the precipitation of the syndrome among which may be: a congenitally inadequate nervous constitution, the additional nervous instability of adolescence, injudicious and radical reducing diets, loss of appetite following illness or surgical operation, hysterical self-inflicted starvation to attract attention or sympathy, psychic trauma from such causes as disappointment in love or marriage, death of a friend or relative, over-industry in school or college, fear of eating arising from manifestations of functional nervous disturbances of the gastrointestinal tract such as hysterical dysphagia and functional indigestion. Fear of being thrust out of a sphere of protection formed by the illness may form the greatest obstacle to recovery. Sheldon<sup>12</sup> has advanced the belief that some cases have a pituitary abnormality and that there is a "special body-mind type" which is peculiarly apt to develop anorexia nervosa in response to emotional difficulty.

Table 1 is a summary of the findings in 27 cases of anorexia nervosa.

In several cases considerable study was directed toward blood chemistry, especially in regard to sodium excretion and blood levels of sodium, potassium, calcium, phosphorus, iodine, cholesterol, urea, and uric acid, but nothing of significance was encountered.

Repeated urinalyses were insignificant, and the blood Wassermann and Kahn tests were done in all and were negative in every instance.

B. *Basal Metabolic Determinations.* Twenty-four of the 27 cases had basal metabolic determinations, and the determinations recorded in the table were the lowest obtained during the period of observation. The number of cases within various levels were as follows:

Number of Cases	Range of B.M.R.
2	0 to —10%
5	—10 to —20%
10	—20 to —30%
4	—30 to —40%
3	—40 to —43%

Benedict<sup>26</sup> presented studies made in regard to the basal metabolism as affected by starvation in his subject, Levanzin, whose basal metabolic rate after 21 days of fasting fell to —30 per cent. Lusk<sup>27</sup> calculated that the fall in metabolism in this subject was caused not only by the decreased body and protoplasmic mass, but also by some specific and unknown factor which tends to protect the organism from the evil results of starvation. This protective mechanism offered by the body explains why the patients with anorexia nervosa have continued to survive on very low caloric diets. Other writers have reported very low basal metabolic rates in cases of anorexia nervosa, and the lowest basal rate that we have found recorded was that quoted by Sheldon<sup>12</sup> in Wittkower's case, in which the rate was —76 per cent.

Joslin<sup>28</sup> has done a total of 661 basal metabolism tests on a series of 113 cases of diabetes mellitus, and in a group of 20 cases with extreme loss of 35 per cent of body weight, the metabolic rates fell an average of 25 per cent (a loss of 0.63 per cent in metabolism for 1 per cent body weight). He contrasts this with the students studied by Benedict, who lost only 10.5 per cent in weight, with an average fall in metabolism of 19 per cent (a fall in metabolism of 1.8 per cent for each 1 per cent body weight). Joslin believes that this difference is due to the fact that normal men have a quicker loss and a quicker adaptability. It is interesting to note that the lowest basal rates in diabetics were found in girls from 16 to 18 years of age, one of whom gave a reading of —48 per cent, and this age is very common for the onset of anorexia nervosa.

C. *Glucose Tolerance.* The glucose tolerance was determined in 18 cases of this series. The method used was as follows: One hundred grams of glucose in water were given orally. Venous blood and urine specimens for glucose determinations were collected fasting and at one-half, one, two,



FIG. 1. *Case 2.* Age 24 years, height 61 inches, weight 65 pounds, weight loss 62 pounds in 5 years.

and the heat production per kilogram of body weight and per square meter of body surface was about 18 per cent lower than at the beginning of the study. The pulse rate was greatly lowered, some morning rates were reported as low as 33 per minute. Systolic and diastolic pressures were distinctly lowered, rectal temperature remained normal. There was a slight falling off in strength tests, but muscular efficiency did not seem to be impaired; in fact, actual measurements proved that on account of their lower weights they were able to walk a mile with less expenditure of energy than

intake for 12 days, this patient had a normal blood sugar level two and one-half hours post prandial, and glycosuria had disappeared.

Previously a great deal of significance has been attached to the low flat tolerance curves as pointing towards the diagnosis of Simmonds' disease. It has been reported by us<sup>20</sup> and others that the glucose tolerance is very

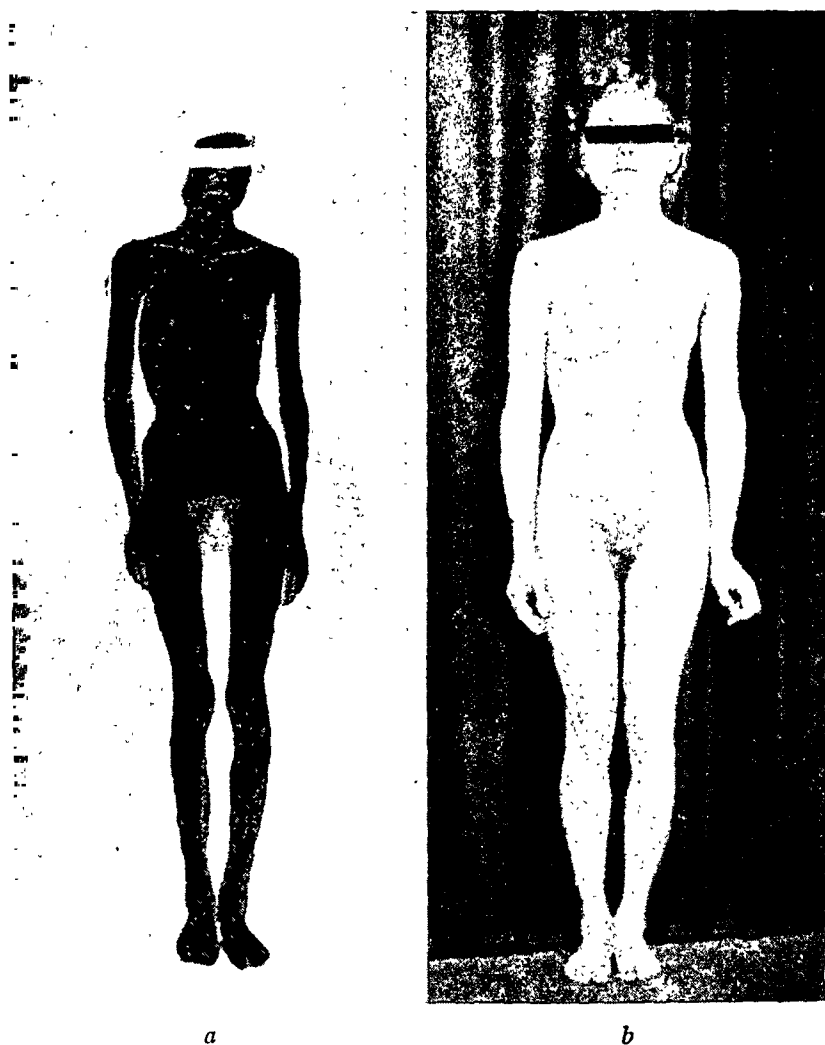


FIG. 6. (a) Age 20 years, height 62 inches, weight 69 pounds. Weight loss 31 pounds in 10 months. (b) Nine years later. Height 62 inches, weight 95 pounds (gained in 6 months).

definitely altered by the dietary intake in cases of diabetes and in functional hypoglycemia. In such patients on maintenance diets we found that the tolerance can be increased by increasing the carbohydrate intake and decreased by decreasing it as judged by repeated tolerance tests. The same type of change apparently occurs in some cases of anorexia nervosa as illustrated by case 14. Sweeney<sup>30</sup> has shown definite changes in the tolerance

stances, although definite data are not available from the records, letters from the attending physicians indicated that they continued to lose weight and both lost more than half their body weight. In case 6 an incomplete autopsy was performed and no cause for death could be found. The adrenal glands were normal; the pituitary gland was not examined. There was no

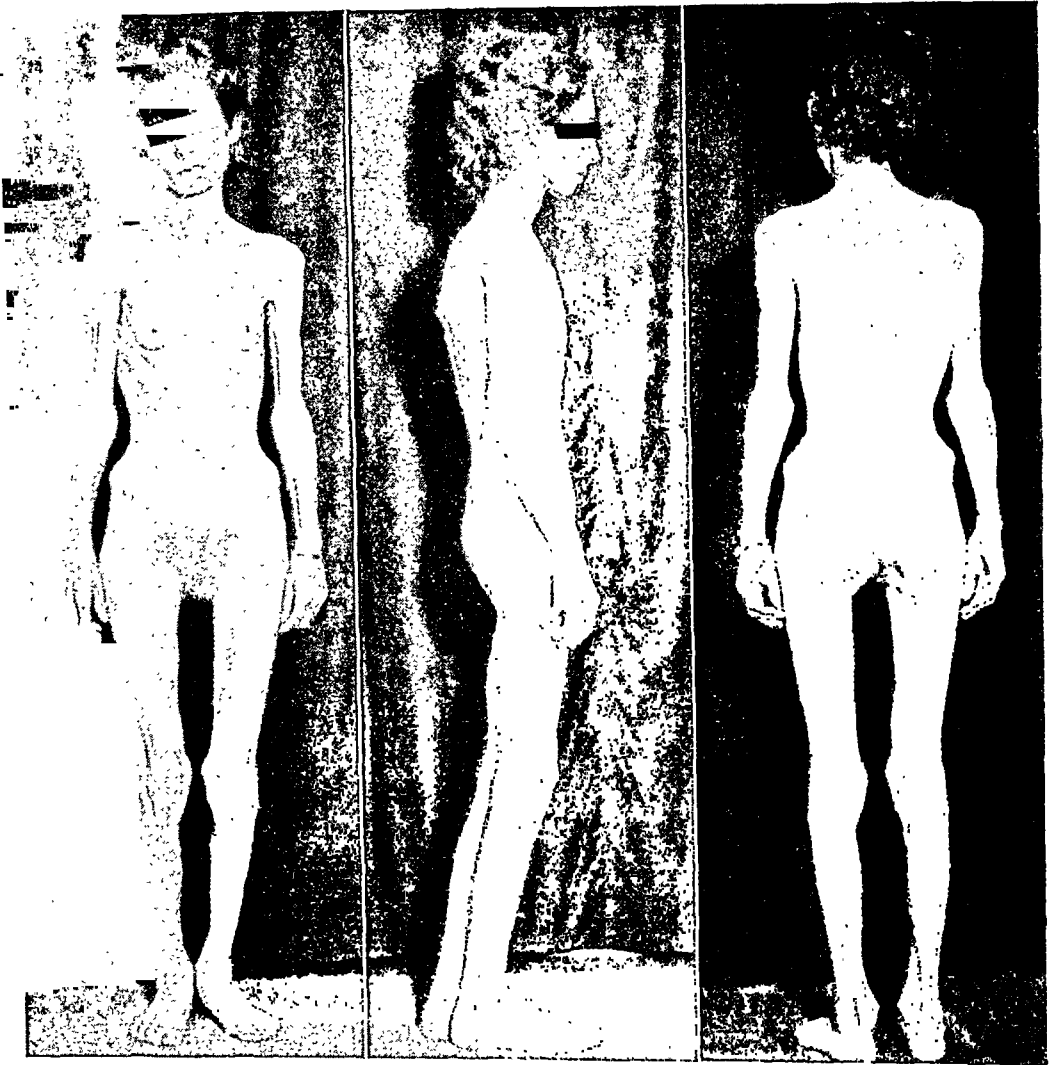


FIG. 3. Case 3. Age 34 years, height 60 inches, weight 59 pounds, weight loss 59 pounds in 10 years.

postmortem examination in the other fatal case. Usually if an individual loses more than one-half of the body weight the outcome is likely to be fatal. In one of our cases, body weight decreased from 188 to 70 pounds, following which the patient recovered and weighs 130 pounds at the time of this writing.

*C. Amenorrhea.* Amenorrhea is one of the cardinal symptoms in anorexia nervosa. Seventeen of our 27 cases had complete amenorrhea; five



gastrointestinal tract. Chest films were made in 21 cases. Evidence of arrested pulmonary tuberculosis was found in only one case.

Roentgen examination of the skull in 15 cases showed no evidence of pituitary disease.

### DIFFERENTIAL DIAGNOSIS

It is extremely difficult and often impossible to differentiate anorexia nervosa and pituitary cachexia during life. Some similarities and differences in these conditions are mentioned below and other conditions more readily separated are discussed briefly.

(1) Simmonds' disease. The fatal syndrome of progressive weakness and cachexia, which was noted by Paulesco in 1907 following the removal of the pituitary gland, has been described in man prior to that date. It was not appreciated, however, that atrophy of the anterior lobe of the hypophysis was the primary etiologic factor until Simmonds called attention to it in 1914.<sup>40</sup> Pituitary cachexia is characterized clinically by: weakness, emaciation, falling of axillary and pubic hair, sensations of chilliness, gastrointestinal atony, atrophic changes in the skin, low blood pressure, low basal metabolism, and disturbance of the sexual functions including the cessation of menstruation, impotence and loss of libido. Pathologically, it is characterized by destruction of the anterior lobe of the pituitary gland, with secondary atrophic changes in the thyroid, parathyroids, suprarenal cortex, reproductive organs, and a decrease in the size of the abdominal organs (splanchnomikre). Various processes have been the cause of the destruction of the anterior lobe, including emboli, thromboses, tuberculosis, tumors and cysts, syphilis, and trauma. The diagnosis of Simmonds' disease is difficult, and we are inclined to agree with Silver<sup>38</sup> who thinks that it can be considered proved only when confirmed at necropsy. Proof of the diagnosis is nearly as complete, however, if it follows operative removal of a pituitary tumor and especially if, following such an operation, careful search at the time of operation fails to reveal any remaining pituitary gland.

The marked cachexia presented by the extreme cases of anorexia nervosa simulates Simmonds' disease very closely. In most instances it is possible to differentiate these conditions with a fair degree of accuracy after continued observation and study, especially regarding the course of the illness as influenced by attempted therapy. We attempt the differential diagnosis on the basis of the following:

D. *Gastrointestinal Symptoms.* Apart from anorexia the most common symptom referable to the gastrointestinal tract is constipation, and this was practically a constant complaint in these cases. The second complaint in order of frequency was "gaseous dyspepsia" described as gas, bloating, feeling of pressure and fullness, all of which occurred after eating. Complete roentgen investigations of the gastrointestinal tract in 11 cases revealed no organic disease to account for the symptoms. Spasticity of the colon was present in the majority.

#### PHYSICAL FINDINGS

A. *General Examination.* The most striking physical change was emaciation in the majority of cases. In addition, there was dryness of the skin, a senile appearance, and evidence of lowered metabolism. In only one case was there definite failure in development of secondary sexual characteristics and that was a fatal case. In an additional six cases there was a decrease in size of the breasts, and the uterus was described as being slightly smaller than normal. In two of these cases modified Friedman tests<sup>21</sup> were done, and were negative. Case 17 was an example in which the breasts were prominent in spite of the obvious under-nutrition. Examination of the fundi oculi and visual fields in 11 cases revealed no evidence of pituitary disease.

None of our cases showed any of the common clinical signs of vitamin deficiency. This is in accord with the observations of others. Bruckner, Wies, and Lavietes<sup>22</sup> state that in complete starvation specific vitamin deficiencies have not been noted, probably because the reduced energy requirements are satisfied by body tissues which are complete foods. It is probable also that the low level of metabolism in anorexia nervosa diminishes the requirements for vitamins.

B. *Blood Pressure, Pulse, Temperature.* In reviewing the table one readily observes a general lowering of blood pressure levels. Pulse rates are slow and in some instances temperatures subnormal. These changes are consistent with an attempt on the part of the body to preserve itself by conserving the expenditure of energy.

#### LABORATORY EXAMINATIONS

A. *Blood.* There were 10 cases in the series in which the hemoglobin content of the blood was below 80 per cent. In some cases pallor of the patient was so pronounced as to suggest anemia of rather high grade, and in some of these anemia was diagnosed by the ophthalmologist because of the degree of pallor of the fundi oculi; yet blood counts in the same individuals approached normal or came within normal range.

The sedimentation rate was determined in many cases and in all was within normal limits.

marked improvement with large doses of sodium chloride and adrenal cortical hormone. In Simmonds' disease marked improvement may be observed under such treatment in some cases in crises.

(3) Intracranial lesions, such as neoplasm, will usually be accompanied by neurological findings as well as changes evident in skull roentgenograms or encephalograms.

(4) Malignancy. When malignant disease results in extreme emaciation it is usually associated with more marked anemia and a less striking fall in basal metabolism than is found in this condition. In most cases of advanced malignant disease clinical and adequate roentgen studies usually produce adequate evidence of its presence.

(5) Tuberculosis may be excluded on the bases of clinical, laboratory, and roentgen findings. There was one case in our series that apparently developed a mild tuberculosis probably secondary to malnutrition. This is apparently a rather common complication in anorexia nervosa. There was no evidence of tuberculous activity in any of our cases during the period of study recorded.

(6) Hypothyroidism may require consideration because of the existence of a very low basal metabolic rate. The hypometabolism in anorexia nervosa is due, we believe, entirely to starvation. In anorexia nervosa dryness of the skin and hair, and brittleness of the nails are common, as in hypothyroidism. Neither edema nor paresthesia was present in any of our cases of anorexia nervosa, whereas in cases of hypothyroidism with metabolic rates lower than minus 25 per cent, some evident edema about the eyes or hands is the rule. In anorexia nervosa the patients often appear to be very active mentally and physically, and their memory may be very accurate in contrast to the lowered mental vigor in thyroid deficiency. There is no marked tendency in hypothyroid states to the weight loss that is always prominent in anorexia nervosa; and finally, thyroid therapy is specific in hypothyroidism but produces little if any clinical improvement in anorexia nervosa.

## TREATMENT

1. Reassurance and psychotherapy. The most important single phase of treatment is that of complete reassurance to the patient that organic disease is absent. A thorough examination is of considerable assistance in impressing the patient that organic causes have been excluded. Following this it is important that a definite diagnosis be reached. The patient and relatives should be impressed with the confidence of the physician in his own opinion. This establishment of complete confidence in the patient, explicit instructions, and firm handling are the most important features of successful management.

2. Diet. A high caloric and high vitamin diet should be insisted upon, and if necessary, tube feedings may be used in extreme cases. The use of a flexible latex tube containing a small bougie to maintain patency may be used,

three and four hour intervals, the blood sugar being determined by a modification of the Myers-Bailey method.

In our patients we found the abnormal tolerance curves to be of two types: (a) decreased tolerance or a diabetic type of curve, in which the second and third hour determinations are high. The curve does not drop

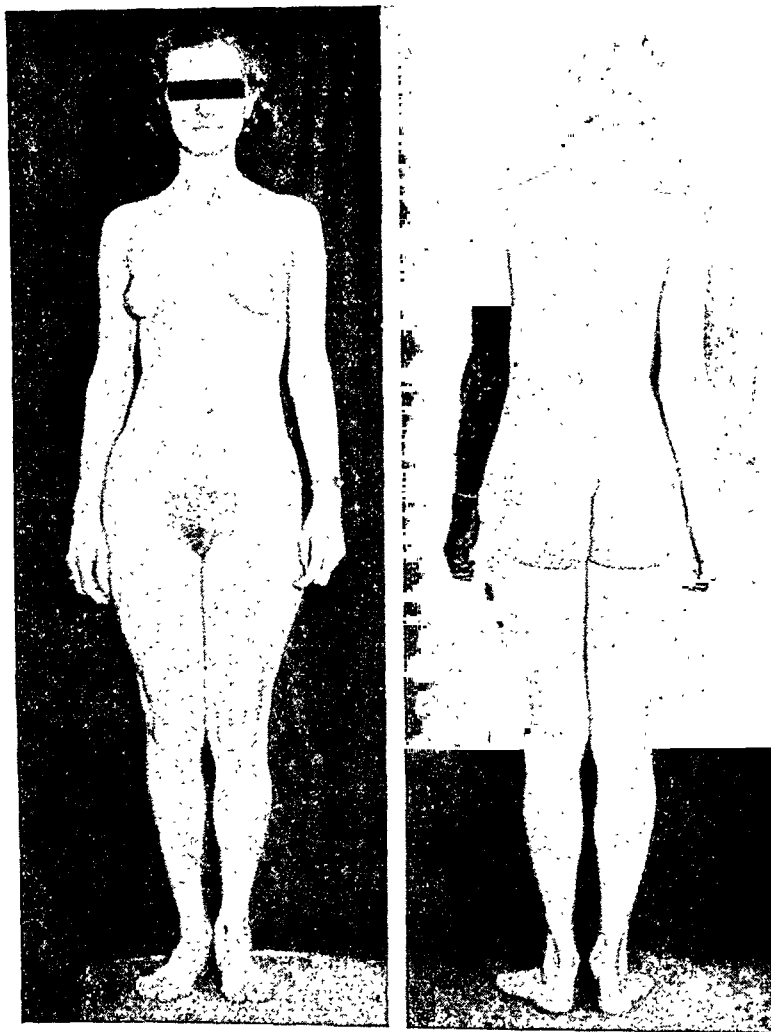


FIG. 5. *Case 10.* Fourteen months later. Height  $65\frac{1}{2}$  inches, weight 122 pounds.

to within normal limits completely at the fourth hour in some instances; and (b) increased tolerance or the low flat curve. This is the type of curve which has usually been referred to as a characteristic finding in pituitary cachexia. There were eight cases that revealed an increased tolerance, while four cases showed a distinctly decreased tolerance. In case 3 it will be noted that the curve is typically diabetic, and it is interesting to note that after following a high carbohydrate intake and a total of 3,000 calories daily

## DISCUSSION

Many cases have been reported as Simmonds' disease in the literature with favorable responses to endocrine therapy. In the light of our experience of striking failure of response to available endocrine preparations over long periods of time, we believe that such cases usually represent, in reality, anorexia nervosa. Richardson<sup>21</sup> pointed out this likely possibility. In view of the greater likelihood of cases presenting themselves with this syndrome as caused by malnutrition than by having actual pathologic changes in the pituitary gland, we feel more caution should be exercised in making the diagnosis of pituitary cachexia.

Case 1 is a very good illustration of mismanagement of a case of anorexia nervosa. Here much dependence was placed upon endocrine therapy and adequate dietary intake was not forced. There may be other cases similarly mismanaged with fatal outcome, the fallacy being that while the attending physician is busying himself injudiciously in prescribing and depending upon endocrine therapy, he may accidentally overlook the real cure; namely, proper psychotherapy and the forcing of a high caloric intake.

In view of the very close similarity of anorexia nervosa and pituitary cachexia, the question arises as to whether dysfunction of the pituitary gland could be a reality and be secondary to nutritional factors. When general bodily nutrition is very poor all tissues must suffer to some degree and the glands are no exception. It is known that certain nutritional factors are of considerably greater importance than others in respect to pituitary activity. Experiments such as those of Parkes<sup>34</sup> indicate that such is the case. He showed that rats with normal estrous cycles became anestrus when fed a diet deficient in vitamin B. Transplantation of the pituitaries of such animals into young females indicated that the glands of the vitamin B deficient animals had less gonad-stimulating action than normal pituitaries.

The systematic investigation of the effects of dietary deficiencies on mammalian reproduction, and particularly on the estrous cycle was initiated by Evans and Bishop<sup>35</sup> (1922) with the aid of the vaginal smear technic. They showed that underfeeding of rats with an otherwise complete diet results in general aberration of the ovulation cycle; they further found disturbance of the cycle on unbalanced diets, and on diets deficient in salts. On diets deficient in vitamin A, rats showed abnormally prolonged estrous symptoms, whereas the absence of vitamin B resulted in a complete cessation of the estrous cycle.

More recently Barrie<sup>36</sup> has produced experimental evidence that suggests that vitamin E deficiency in rats causes failure of the normal reproductive process, of lactation, and of activity of the thyroid gland and that this is associated with deficiency in production of gonadotropic and thyrotropic hormones by the anterior lobe of the pituitary gland. This evidence was further substantiated by the histological findings. The conclusion drawn by Barrie is that vitamin E is necessary for the normal function of the anterior lobe of the pituitary gland.

curves following rigid dietary management for only two days in normal subjects. Sheldon<sup>13</sup> has recently discounted the significance that he had formerly attached to the flat type of tolerance curve seen in some of his cases of anorexia nervosa, and has reported a case of anorexia nervosa in which he has manipulated the curve by dietary control alone. Ross<sup>14</sup> recently recorded his observations on a case of anorexia nervosa with special reference to carbohydrate metabolism, and he believes that some liver preparations which he used in his patient have some influence on the regulation of the carbohydrate metabolism of these patients. We believe that the significance of glucose tolerance curves must be measured in terms of the diet used habitually for days or weeks preceding the test, and it is likely that there are other factors which influence this determination that are as yet unrecognized. Recent work has been done in an effort to detect the relation of vitamin B<sub>1</sub> to carbohydrate metabolism, and may prove to be of some importance.

*D. Hormonal Assays.* The gonadotropic hormone assays in this series were determined by a modification of the Friedman test,<sup>31</sup> which method gives a roughly quantitative determination. Assays for urinary estrogens were done by a method described by Cuyler,<sup>32</sup> except cases 4, 5, 7, and 18 which were done by the Kurzrok method.<sup>37</sup> The normal levels of urinary estrogens excreted in 24 hours vary usually from 20 to 50 rat units daily as estimated by the first method, 4 to 19 units by the second. Urinary androgen assays were done according to the modified Gallagher and Koch method as described by McCullagh and McLin,<sup>33</sup> the normal value for which is 18 to 80 international units per 24 hours.

The results of the bio-assays done are given in the table. It is not surprising that bio-assays in these individuals should show very low titers for estrogens since amenorrhea is so common. In 13 cases urinary estrogen levels were determined and only two approached average normal levels, whereas 11 cases showed a very definite decrease in the estrogen excretion.

It appears significant that among 18 cases in which qualitative gonadotropic hormone assays were done, an excess of this material was shown very definitely in seven cases, and a measurable amount was present in three. This seems to us to be very strong evidence against pituitary insufficiency as a cause of the symptoms, and appears to be a finding quite inconsistent with pituitary gland failure of an extent capable of producing pituitary cachexia. These findings strongly suggest the fact that the nutritional disturbance affects the ovaries directly rather than through the medium of the pituitary, and that the prolactin excess is an evidence of compensatory pituitary hyperactivity. The women having excessive urinary gonadotropic hormone are noted to be cases in which the amenorrhea is of long standing in each instance, which lends still further support to this view.

*E. Roentgen Examination.* There were no positive findings except spasticity of the colon obtained in any of the roentgen examinations of the

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## DIFFERENTIAL DIAGNOSIS

## Simmonds' Disease:

1. Age incidence: More common in adult women during child-bearing period.
2. History: Good health until onset; often history of puerperal sepsis, syphilis, trauma, or symptoms suggesting tumor.
3. Symptomatology:
  - a. Weakness is pronounced.
  - b. Anorexia is unassociated with neurotic trends.
  - c. Digestive symptoms less marked.
  - d. Amenorrhea usually is a matter of slight concern.
  - e. Severe crises may occur causing death.
4. Physical signs: Definite failure in the secondary sex characteristics, atrophy of breasts, uterus, etc. Loss of axillary and pubic hair.
5. Neuropsychiatric: Dull appearance, poor memory, and intellectual impairment. In some cases spastic contractures of the limbs occur.
6. Laboratory evidence:
  - a. Low B.M.R.
  - b. Glucose tolerance increased as the rule.
  - c. Roentgen evidence of erosion of the sella as seen in tumors, trauma, luetic lesions, etc., may be present.
  - d. Visual fields—defects likely with tumor.
  - e. Hormonal assays:
    1. Gonadotropin assays—theoretically always very low. No measurable gonadotropin in one postoperative case studied by us.
    2. Estrogen or androgen assays: Theoretically always decreased.
7. Course: Progressively downhill with lack of response to all endocrine therapy available at this time.
8. Prognosis: Grave, though some cases live many years.
9. Pathology: Almost complete destruction of the anterior lobe of the pituitary with secondary atrophic changes in other endocrine glands, viscera, and skin.

## Anorexia Nervosa:

1. Age incidence: More common in adolescents and between ages of 16 and 24 years.
2. History: Psychogenic background, and often a definite precipitating factor can be elicited.
3. Symptomatology:
  - a. Strength is surprisingly well preserved in spite of emaciation.
  - b. Anorexia and emotional disturbances are intimately connected and a marked aversion to eating may be recognized.
  - c. Functional indigestion is more prominent.
  - d. The amenorrhea as well as other features may be matters of great alarm to the patient and relatives.
  - e. If death occurs it follows typically, slowly progressive changes.
4. Physical signs: The breasts often escape the wasting until the final stages. Axillary and pubic hair are usually spared.
5. Neuropsychiatric: Usually impulsive; much more alert mentally; hysterical trends.
6. Laboratory evidence:
  - a. Low B.M.R.
  - b. Glucose tolerance may be increased or decreased.
  - c. Roentgen evidence absent.
  - d. Visual fields—normal.
  - e. Hormonal assays:
    1. Gonadotropin assays (Friedman test) may be positive or show measurable gonadotropin exceeding the normal. (However a negative test cannot be considered diagnostic).
    2. Estrogen and androgen assays: Usually but not always decreased.
7. Course: Response to psychic and dietary therapy, and forced tube feedings if necessary.
8. Prognosis: Dependent chiefly upon accurate diagnosis and energetic treatment.
9. Pathology: All available data suggest that there are no characteristic changes in the endocrine glands or other organs.

(2) Addison's disease may be difficult to exclude at times, but the absence of pigmentation of the skin and mucous membranes, and a negative salt deprivation test with a high potassium intake, as suggested by Wilder et al.,<sup>39</sup> are good evidence against Addison's disease. Normal blood sodium and potassium levels are usually seen in anorexia nervosa, and there is no



and labor loss have brought out the important fact, that for every patient in whom nervousness or emotional conflict is readily obvious or elicited in the course of medical history and examination, there is at least one in whom it is extraordinarily well concealed. This is particularly likely to be the case when the patient has an actual somatic disorder. We ourselves were surprised in the early period of our study to find that more than half of the patients in whom we were able to demonstrate that the emotional component played a major rôle appeared both to themselves and to the attending physician to be completely normal happy human beings. Our own and other studies have called attention to the frequently inverse relationship of physiological and psychological symptomatology. For example, many of our "completely normal happy" people became neurotic when they were "cured" of their somatic disorder, and it was among this group that relapses were the most frequent.

#### EMOTIONAL COMPONENT IN PATIENTS WITH CARDIOVASCULAR DISEASE, DIABETES, FRACTURE

As will be seen from table 1 (which gives figures for three of the groups studied from July 1, 1934 to July 1, 1938) an average of 50 per cent of all the patients in these groups of serial admissions was found to be unsuitable for study on the basis of such factors as (a) death shortly after admission;

TABLE I  
Patients in the Total Admission Groups Excluded from Detailed Investigation

	Cardiovascular Disease 1934-1938 out of 748	Diabetes 1934-1938 out of 148	Fractures 1934-1938 out of 232	TOTAL 1128
Reason for Exclusion:				
I. On the Basis of Illness or Defect:				
(a) Death shortly after admission.	114	7	0	121
(b) Other primary complicating disease.....	164	20	17	201
(c) Psychosis.....	6	0	2	8
(d) Low mentality.....	17	1	7	25
II. On the Basis of Feasibility:				
(a) Referral elsewhere for chronic or terminal care.....	34	4	2	40
(b) For some reason not to be re-admitted.....	9	2	1	12
(c) Transferred to the private service, referred to local physicians, or otherwise impossible to follow.....	66	21	49	136
(d) Language difficulties.....	16	1	3	20
TOTALS.....	426	56	81	563
Percentage of the total admissions both years excluded.....	(57.)	(38.)	(35.)	(50.)

and solutions of condensed milk will avoid clogging from milk curds. The fluid intake and deficient calories may be made up by the use of extra feedings or of glucose in saline intravenously.

3. Vitamins. We routinely add vitamin preparations by mouth, and more recently have been using crystalline vitamin B<sub>1</sub> preparations combined with liver extract as injections intramuscularly.

4. Endocrine preparations. In our cases there were many patients who were considered "pituitary failure" at the onset of the illness, and consequently many endocrine preparations, notably pituitary extracts, were given with the hope of favorable response. There were three cases in which continued and energetic use of many endocrine preparations resulted in continual downhill progression of the illness, and after discontinuance of this type of therapy and the instigation of forced dietary intake with added vitamins, we have observed favorable responses. There were a few cases that received endocrine preparations and maintained an adequate dietary intake at home that responded favorably, but in light of the failure in the other cases observed closely, we believe that dietary therapy was the cause for this response. With regard to thyroid, we consider the hypometabolism to be a compensatory and protective mechanism in most of these cases, and believe that thyroid is contraindicated where the weight is low since any increase in metabolism retards weight gain, which is of prime importance in the treatment. If hypometabolism remains after a normal weight is attained, and especially if amenorrhea still exists, the use of thyroid may be worthy of reconsideration.

Many of these cases show a rather definite sensitivity to insulin. If it is to be used, careful discrimination is advised. The response to insulin was of doubtful value in our cases and we feel that its value in this disease is decidedly limited.

In some of our cases the maintenance of normal weight and general good health for months has been associated with continued low urinary estrogens and persistent amenorrhea. In consideration of this we believe that some permanent damage to the ovaries may have occurred in some cases, particularly those of long-standing. In such instances gonadotropic or ovarian therapy is to be given serious consideration.

### PROGNOSIS

The earlier the diagnosis and the sooner appropriate treatment is arranged, the more favorable the prognosis. It is generally agreed that none of these cases is hopeless while life exists. In this series there were two fatalities, and in both instances it was impossible properly to control the patients and the dietary intake. Tuberculosis is a relatively common complication in cases of anorexia nervosa and with this added, the prognosis is grave.

Every physician in practice knows in general what is meant by these statements relative to bodily changes accompanying emotion but the subject has been made more concrete by recent psychosomatic studies; for example, by the research of investigators like H. S. Liddell who, following some clues provided by Pavlov was able to demonstrate similar phenomena in animals.

In Liddell's laboratory the following observations were made on animals which had been adjusted to laboratory conditions and trained in accordance with the conditioned reflex technic. It was found that if such an animal listens to a metronome and is fed when the metronome has a rate of 120, but at the rate of 50 is given no food, this animal readily learns to distinguish between the two and opens the food box only when the metronome has the proper rate. If then the rate of the slower metronome is increased to 80 or 100, so that it becomes difficult or impossible to distinguish between the two rates, many animals develop a constant state of tension. At the same time the heart rate increases, the heart may beat irregularly or develop extra systoles, and the animal shows similar disturbances in other bodily functions. The interesting thing is that after the animal has been subjected to the strain of attempting to make this discrimination it may no longer be able to distinguish between even a very slow and a very fast metronome. It seems to become worried; minor disturbances in the barnyard which never troubled it before become problems; it ceases to get along well with other sheep or pigs and is unable to relax at night. If then, such an animal is turned out to pasture and left alone with the others for a year or more the heart may quiet down, but animals were observed that when brought back to the laboratory in which this difficult problem was presented to them, at the first sound of the metronome or sometimes even on entering the laboratory, developed trembling, palpitation, and all the other physical disturbances experienced before. If you did not know, you would jump to the conclusion that they had been badly frightened there.\*

Psychologists have been interested in the question: Under what circumstances may the normal physiological accompaniments of emotion become pathogenic? Relative to this point we have the following observations:

1. Such physiological changes may persist over a long period of time or become chronic when the associated emotion or conflict is inadequately discharged in appropriate action.

2. The associated emotion or conflict is particularly likely to be inadequately discharged if the individual has an inadequate appreciation of the problem with which he is faced, or is thwarted in solving it. (Under such circumstances he may even try to put the whole problem out of his mind and pretend it does not exist.)

This latter, of course, creates a problem in history taking. It has been said that every medical history of a patient contains three parts: what the

\* One might wonder why the sheep was so disturbed by all this, why it did not simply open the food box whenever the metronome sounded knowing it would find food sooner or later. But this statement must be modified to the following extent: A sheep left free in the pasture and taught a maze with the finding of more food as a goal, when the problem becomes too difficult for it it simply lies down or grazes, showing no further interest. What makes the sheep susceptible to development of the neurotic type of behavior described when frustrated in its expectation or unable to distinguish metronome rates, seems to be the fact that it has already given up a good many degrees of freedom in its submission to the laboratory situation. This seems to have a bearing on neurotic types of behavior developed by human beings who have given up a good many degrees of freedom by submission to cultural patterns.

It appears logical to suppose that in anorexia nervosa, where malnutrition plays the master rôle, there should be some effects from a lack of vitamins, and that lack of vitamins A, B, and E may contribute toward the development of the syndrome. The finding of large amounts of gonadotropic hormone in the urine in the presence of anorexia nervosa, however, appears to indicate that neither lack of vitamin B nor any other factor is causing pituitary sex hormone deficiency. If any specific nutritional factors are more intimately connected than others with gonadal deficiency, the effect would appear more direct upon the gonads and the excess of gonadotropic substances as shown by the Friedman test in our cases represents a compensatory pituitary hyperactivity. Until more definite knowledge is available, and especially since there is no obvious reason to believe that pituitary deficiency exists, it would seem wisest in the treatment of these cases to concentrate our attention upon the promotion of normal nutrition.

#### SUMMARY AND CONCLUSIONS

1. A brief summary of the literature and the findings in 27 cases of anorexia nervosa are presented.

2. The etiology, clinical picture, symptomatology, results of investigation, treatment, and prognosis are given with special emphasis on the similarity between anorexia nervosa and Simmonds' disease.

3. Concerning differential diagnosis, an important feature is the demonstration of an increased, gonadotropic hormone excretion in some cases of anorexia nervosa, a finding which is not consistent with severe pituitary failure.

4. It is suggested that vitamin deficiency may be a factor in producing the gonadal failure found in anorexia nervosa.

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for more than half of our total mortality and disability today. In other words, they make up the bulk of every physician's practice.

### CORRELATIONS BETWEEN PERSONALITY AND ILLNESS SYNDROME

Even more interesting than the high percentage of patients in whom we found the emotional component in the illness important, however, were our observations concerning the types of persons that succumb to different types of illness. Of course we mean by this personality in terms of physical as well as psychological make-up. Patients in each of the disease groups studied showed fundamental similarities in the constellation, somatic make-up, major emotional conflicts, character resistances or characteristic ways of dealing with problems. They differed in these respects from patients in each other group studied although no factor was definitive.

Differences in this constellation seemed to be important:

*First*, because they were present in a high percentage of patients in each group in contrast to patients in other groups.

*Second*, because they could be shown to bear a close relation to the symptoms in question, often understandable in terms of physical changes accompanying emotion.

*Third*, because psychotherapeutic attention to them even without correction of other personality difficulties produced changes in the symptoms, first exacerbation when the material was brought up, and second relief as the material was worked through.

*Fourth*, because follow-up of patients with symptoms suggestive of certain of these illnesses and the related psychic problems has shown in some cases that the illness suggested by the symptoms had actually developed. This seemed to be particularly frequent where the psychic component of the illness was prominent and characteristic. Illustrative cases have been published elsewhere.<sup>2</sup>

Only a sketchy impression of these differences can be given but it is significant that many of them were differences that could be determined by any statistician who reviewed the medical charts. Their detection not only required no psychiatric training but also required little or no medical training. The differences under this category are differences in educational and occupational history, income, and early disease history. Although these points were checked only at the close of our study they are mentioned first because of their objectivity and because of their (to us, surprising) corroboration of our conclusions from the personality studies.

Chart 1, where each different shading represents a different disease group, shows the marked divergency of one group as compared with another. It may be interesting to note that our base line from which plus and minus deviations are determined represents the upper 60 per cent of the population. Using as a base line, educational averages for the total popula-

# EMOTIONS AND BODILY CHANGES; A REPORT OF SOME RECENT PSYCHOSOMATIC STUDIES\*

By FLANDERS DUNBAR, M.D., Ph.D., Med.Sc.D., *New York, N. Y.*

A DISTINGUISHED member of this College made a statement some years ago which has served as both guide and inspiration to many of us who have turned our attention to problems of psychosomatic medicine. After it had been discovered what diverse illnesses might have an important source in emotional conflict, a controversy arose which reached its height a decade or so ago between proponents of psychogenesis versus physiogenesis of disease. It was against the background of this controversy that Dr. Walter B. Cannon made the comment

An escape from the insistent demands of the pathologist for morphological evidence of disease, and also from the vagueness and mysticism of the psychological healers, can be found, I am convinced, in an understanding of the physiological processes which accompany profound emotional experience.

It was in these terms that we undertook to study in a general hospital† groups of patients suffering from different types of illness. After a preliminary review of cases showing combined medical and psychiatric problems it was decided that a better perspective would be obtained by studying serial admissions to the hospital in different disease groups whether or not any emotional problem appeared to be present. Over a period of ten years this investigation covered 1500 patients. These patients were observed simultaneously by way of the technics of physiology and clinical medicine, and the methods of medical psychology. The routine study of all admissions to the hospital for cardiovascular disease, diabetes, and fracture, as well as for some allergic and gastrointestinal disorders (in the age range 15 to 55) revealed an important psychic component in approximately 80 per cent‡ of the patients who entered the hospital in a condition which made such study feasible.

Most estimates made by internists in this country, as well as by physicians operating under National Health Insurance in Great Britain, have given this figure as 34 to 40 per cent. But careful studies of industrial sickness

\* Read at the Cleveland meeting of the American College of Physicians, April 5, 1940.

† In the department of medicine at Columbia University with the coöperation of the departments of psychiatry and surgery and aided by a grant from the Josiah Macy, Jr., Foundation.

‡ The 80 per cent of patients in whom this appeared to be the case were divided into the following groups:

1. Those in whom the psychic component was primarily a reaction to the illness itself—less than 5 per cent;
2. Those in whom it was a complicating factor affecting the course of illness and response to treatment—75 per cent;
3. (A subdivision of 2.) About 50 per cent in whom the psychic component was of demonstrable etiological significance in the development of illness.

Chart 2 makes it possible to analyze the differences in educational history of the fracture group as compared with the coronary and angingal groups. All these groups have a higher educational average than that of the upper 60 per cent of our total population. Incidentally, the fracture

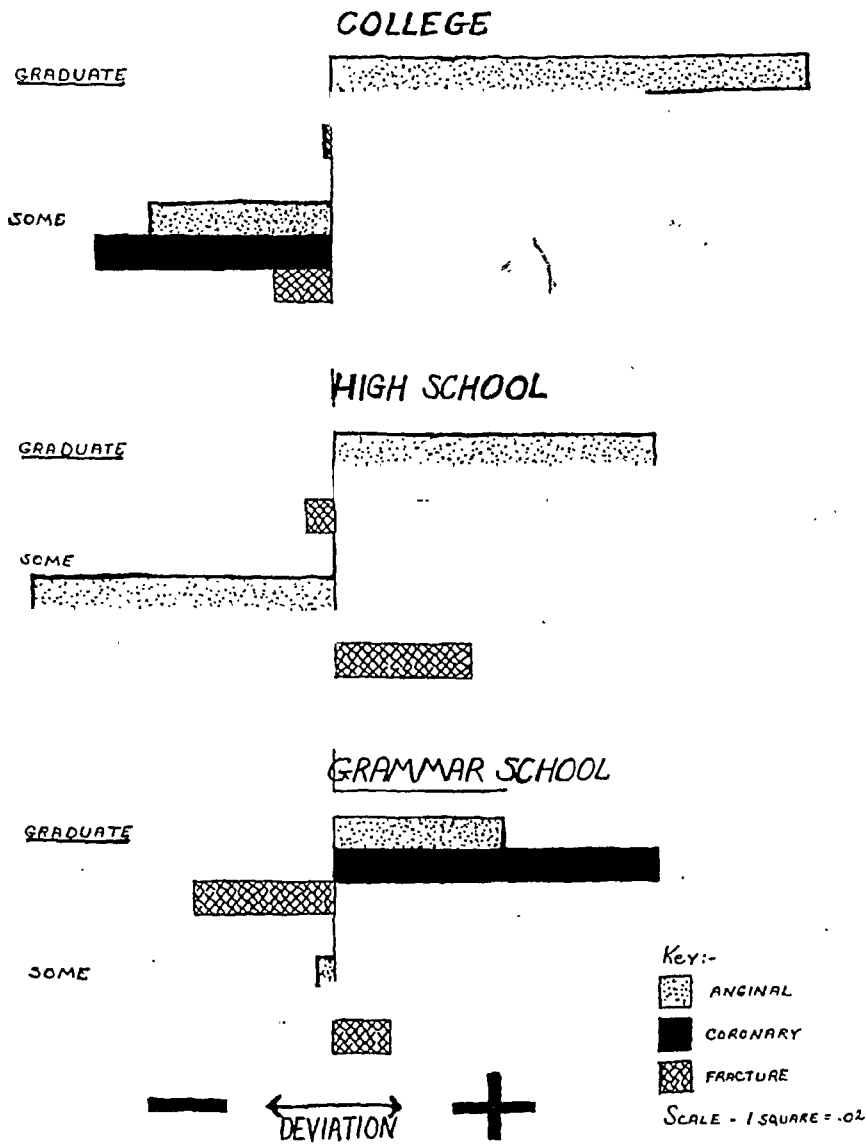


CHART 2. Educations.  
Males—Females 21-55.  
Base—Upper 60% General Population.

group pretty nearly represents the base line for the total number of patients covered in our study; most of the other groups shown on the preceding chart fall below them.

It may be noted that in the three categories representing termination of academic education in the middle of educational unit (that is some elemen-

(b) other primary complicating disease; (c) psychosis; (d) low mentality; or because referral elsewhere made adequate study impossible. It is of some interest that of the patients with cardiovascular disease, slightly more than half were excluded; of the patients with diabetes slightly more than a third; and of the patients with fractures about 38 per cent.

It is interesting with respect to the psychic component (table 2) that the percentages for the two-year periods charted are in such close accord.\* It will be seen that the only significant difference in our figures for the second period of two years as compared with the first was in our estimate of the number of patients for whom psychotherapy was recommended. This is

TABLE II

	1934-1936 Per cent	1936-1938 Per cent	Four Year Period Per cent
OF THE PATIENTS SUITABLE FOR STUDY THE PSYCHIC FACTOR WAS			
Of significance in . . . . .	79.	80.	79.
Inadequately determined in . . . . .	21.	20.	21.
OF THE TOTAL PATIENTS ADEQUATELY STUDIED THE PSYCHIC FACTOR WAS			
Too much complicated somatically or too deep-lying for more than palliative treatment in . . . . .	32.	8.	20.
Such as to warrant psychotherapy in . . . . .	68.	92.	80.

accounted for in part by our omission during the second two years of all patients in the age group 50 to 55 among whom the suitability for study had been found to be much less than in the age group 15 to 50, and in part by our increased skill. We were surprised by the quick response of many of these patients to relatively superficial psychotherapy. Of course the question arises what were our *criteria* for judging whether or not the psychic component played an important rôle in the illness. Before giving these it may be useful to state a few points by way of amplification of the statement made at the outset concerning the perspective from which this study was undertaken.

Physiologists have shown that the bodily changes which are the most closely associated with emotional experience are the same changes that are the most immediate responses to other noxious agents such as bacteria or toxins, that is, changes in tension of smooth or striated muscle, changes in secretion (hyper- or hypo-secretion) and changes in circulation. It goes without saying that these changes may affect the function of any organ in the body, and of course if long persisting may be followed by secondary changes such for example as atrophy, or hypertrophy of the organ concerned.

\* This was unexpected both because of the nature of the problems we were studying and because during the four-year period we were covering there were changes in our research staff involving study of patients by several different physicians with different training and personality. Tables 1 and 2 are reprinted with permission from the *American Journal of Psychiatry*.



with coronary occlusion and with the anginal syndrome without demonstrable coronary disease were markedly above them.

What is the bearing of these charts on the problems we are discussing? What is their significance for psychosomatic medicine? They interested us for the following reasons in terms of our personality studies of fracture patients and patients with coronary disease.

*First*, both groups were in conflict with authority and in both cases the onset of illness coincided with circumstances which made this conflict acute.

*Second*, these two groups of patients had completely different ways of dealing with authority; the former attempted to avoid any type of subjection to authority by becoming adventurers, by frequent changes of environment, occupation, boss and sometimes even wife; whereas the latter tended to stick to one job, usually their first job, for many years, working long hours without vacations until they themselves had become the authority. This tendency was borne out even by the history of marriage and divorce and size of family. Whereas about the same percentage of each group married, the average size of family for the coronary patients was much greater than that for the general population, whereas the average size of family in the fracture group fell far below the average for the general population. The educational charts indicate that this personality tendency toward self discipline and persistence among coronary patients and toward impulsive activity among fracture patients started early in life and was characteristic of the groups in question: the fracture patients had a tendency to leave school in the middle of an educational unit, and the coronary patients only after they had completed an educational unit. Typical case history excerpts are the following:

Fracture Patient: "I had always planned to study engineering. During my third year in High School I discovered that to do this I had to have two languages. This sort of discouraged me. It didn't seem worth bothering about at the time. So I left High School and joined the Navy. I didn't like the Navy but I didn't know just how to resign. Then I had an accident and got out. I worked in a boiler room for a while, then I joined the police force. That didn't go so well because I couldn't stand being bossed, it was just as bad as the Navy. And so, ever since then I've just done odd jobs."

Coronary Patient: "When I was twelve I ran away from home because I couldn't stand being bossed by father. I got a job as an errand boy in a butcher shop and finished High School at night. I worked up in the business until I was a clerk, a manager, and finally I was the boss of the business. I worked 14 to 18 hours a day and never took a vacation. But things went well and now I own a chain of butcher shops in the city."

In the fracture case the accident occurred while the patient who had been out of work for some months was looking for a job. "I was walking across the street with my hat pulled down over my eyes, thinking if I got turned down once more I could never go home and face my wife. I might as well sleep on a park bench."

In the coronary patient the onset of illness followed the acceptance of a partner in business "because it had become too much for one man to manage. But it always rankled because I wasn't my own boss anymore. My heart was heavy and I began to have pains."

patient tells you, what the patient won't tell you, and what the patient can't tell you. It is this third part which is most important for psychosomatic diagnosis.

In our research, one of our major problems was the development of what we have called a psychosomatic history and of technics of eliciting such material. The first objective was to obtain a clear picture of the psychological as well as of the physiological make-up of the patient; the environmental stresses and emotional conflicts to which he had been exposed and his habitual manner of dealing with them. This latter is particularly important because as Sherrington has said, the most satisfactory release of instinctual tension is action, the least satisfactory is thought, and speech stands half-way in between.<sup>1</sup> There is a great difference between the people who on receiving "bad news" dash down to the ball field or to a movie, or to work, as compared with those who take time to go off by themselves and think it all over, or those who call in the neighbors or make a round of visits to their friends to tell them what has happened. The physiological accompaniments of the emotion aroused seem to be different in each case. In our observation, constitutional and other factors being equal, the patient with coronary disease or hypertension inclines to keep his feelings to himself and think whereas the patient with the accident habit has a long history of impulsive action under stress.

The following points were then evaluated as criteria of the significance of the emotional factor.

1. The emotional setting of early attacks as compared with attacks precipitated during interviews.

2. The appropriateness of physiological symptomatology (in terms of our knowledge of physiology) to the conflicts and emotional problems and character differences diagnosed.

3. The diagnostic opinion of five different observers as to the relative importance of the patient's psychic and somatic problems.

4. The patient's improvement or lack of improvement with therapeutic attention to the specific behavior pattern found to be characteristic of the disorder in question (see next section) without reference to modification of the external situation or the patient's total personality adjustment.

5. The patient's ability to stay well (as shown by follow-up visits) in spite of subsequent similar injury by the environment, whether through exposure to infection, or to mother-in-law or loss of job as the case might be.

In the course of this study, we became convinced of the truth of Sir William Osler's statement: that what happens to a patient with tuberculosis depends more on what he has in his head than what he has in his chest, and furthermore, that this statement applies equally well (with appropriate re-phrasing) to patients with cardiovascular disease, diabetes, gastrointestinal disease, allergy or fracture. This is of considerable importance if we realize that the illnesses enumerated (with the addition of nervous diseases) account

When we first studied this question we found little that was significant in the situation preceding the accident in our patients. They were usually worried about a job, "a fight with the wife," being reproved by the priest, and so on. We thought at first that being out of work and having a low income might be a factor, but it is clear from chart 4 that the average income of these patients was above that of the patients with hypertensive cardiovascular disease. Actually it was above the average for the total number of patients studied.

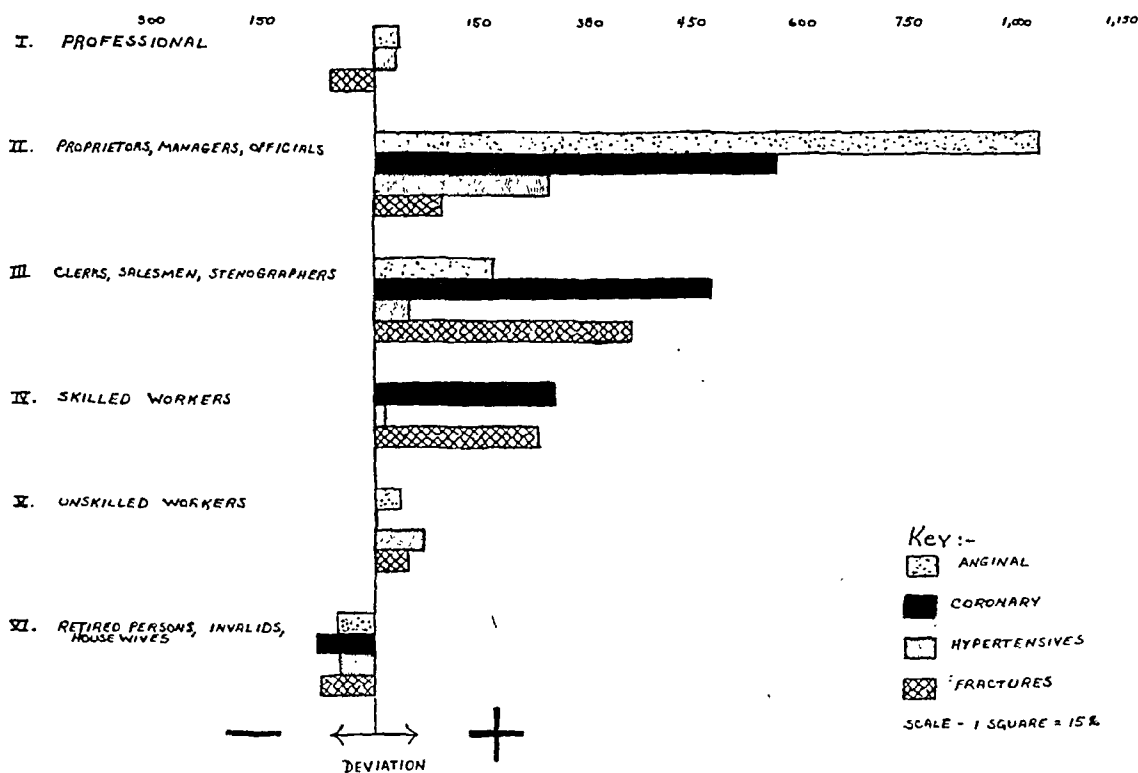


CHART 5. Occupations.  
 Males—Females 21-55  
 Base—General Population.

We thought that perhaps more of them were laborers and so more exposed to accidents. But we found more unskilled laborers among patients with hypertensive cardiovascular disease and more skilled laborers among patients with coronary disease, both of which groups have relatively low accident records. The percentage of "dangerous" jobs was as great among those who had coronary disease as among those who had accidents (see chart 5). These observations lend force to the characteristic of impulsive action under stress (and related patterns which cannot be given here) as a possible clue to the personality factor in accident proneness; in conjunction with the material to follow they suggest also that the opposite characteristic among patients with coronary disease may have a bearing on their illness, too.

tion, all of our groups showed a positive deviation.\* This offers some gauge of the selective factor brought in by the hospital itself. (In order to make our figures comparable with those for the total population which are

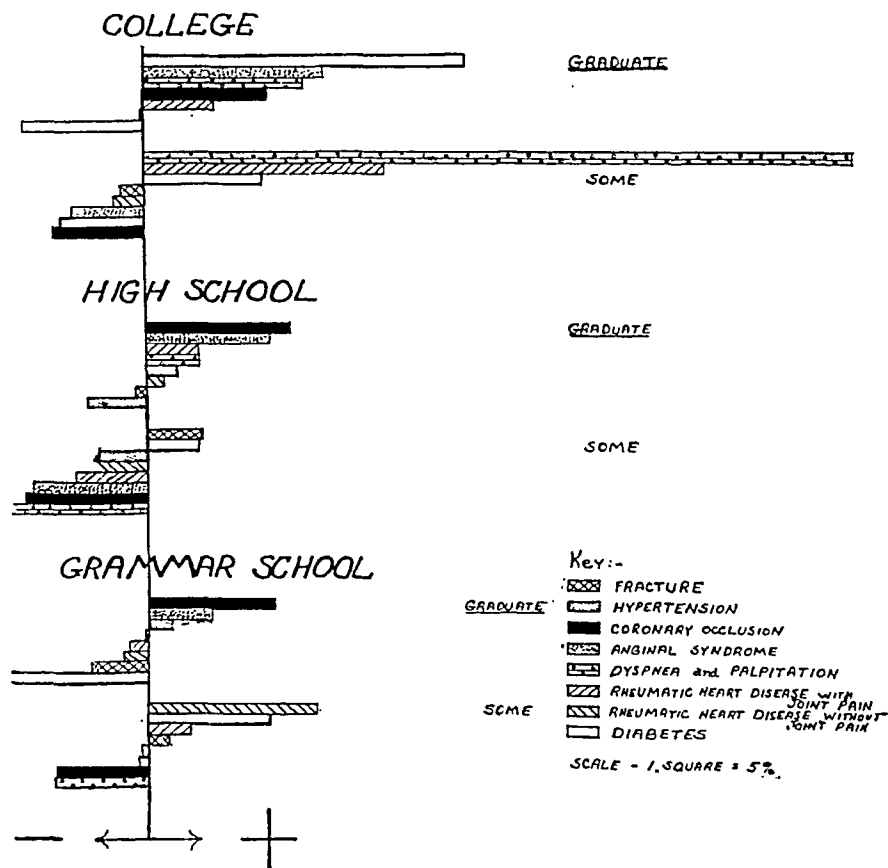


CHART 1. Educations.

Males—Females 21-55.

Base—Upper 60% General Population.

given in terms of persons over 21, we have charted only those of our patients who were over 21. But since all those over 55 are excluded we would expect a higher educational average than that for the general population because educational standards have been higher in the last 30 years than in the preceding 30 years.) We feel, however, that we have an adequate sample at least for our hospital because no significant change occurs in the deviations presented whether a series of 100 or of 150 patients is used for each group.

From this point on the discussion covers only three of the disease groups studied: patients with fracture, patients with coronary disease, and patients diagnosed anginal syndrome but without definite evidence of coronary occlusion. These groups included 430 of the 1500 patients in the total study.

\* With the exception of the elementary school group where a minus deviation is really equivalent to a positive deviation in terms of educational level.

ticular hospital in terms of its geographical and metropolitan location, and the income group it serves. But, whatever later studies may show, it seems to us that these purely objective facts even aside from some very significant observations with regard to conflicts and behavior patterns in these patients indicate psychological and physiological (that is psychosomatic) differences between the disease groups studied. As already noted the charts relative to objective data were made only after we had reached certain conclusions from personality studies of these patients, and we ourselves were surprised to what a degree they were complementary and confirmatory.

### IMPLICATIONS FOR THERAPY

Although in the space allowed it is impossible to discuss therapy, it is easy to see that the accident patient with his tendency to avoid authority and responsibility is likely to become a difficult problem in the hospital especially if he is a compensation case, or if he feels guilty about this tendency to avoid or to act impulsively. The hospital gives him an excuse to be taken care of which he may be inclined to exploit. The coronary patient on the other hand may need to be encouraged to relax and allow himself to be taken care of, and to relinquish a little of his sense of responsibility.

Follow-up of the patients studied, covering a period of from two to ten years, showed a marked difference between patients treated by psychological methods in addition to the clinical routine, as compared with patients not so treated. This difference was in the main in the patients' ability to stay well even though exposed to all the same external difficulties. In the untreated group recurrences of the illness in question, and readmission for a new illness or accident occurred in the majority of cases. In the treated group readmission was rarely necessary. This subject together with statistics is discussed in another publication.<sup>5</sup> This observation seems important since the illnesses studied represent the major causes of disability and invalidism in our population today.

### CONCLUSION

First, we have reported differences in personality, including differences in physiological and psychological behavior patterns in patients with different illnesses.

Second, these seem to have a bearing on the type of illness developed, although in the space allowed, this has not been adequately demonstrated.

Third, Sherrington's comment relative to expression of tension in action vs. expression in thought accompanied by vegetative changes seems to be borne out by the histories of the two groups of patients presented in detail. Similarly evidence is supplied for the laws of emotional economy variously stated by Dr. Adolf Meyer and Freud that emotion which is repressed does not become ineffective but has its effect by way of other channels often involving the vegetative functions.

tary school, some high school, or some college) the coronary and anginal patients show a minus deviation from the upper 60 per cent of the population, but that this is more than compensated by the marked plus deviation in *completion* of the educational unit in question or of a higher educational unit. The *fracture patients* on the other hand show a positive

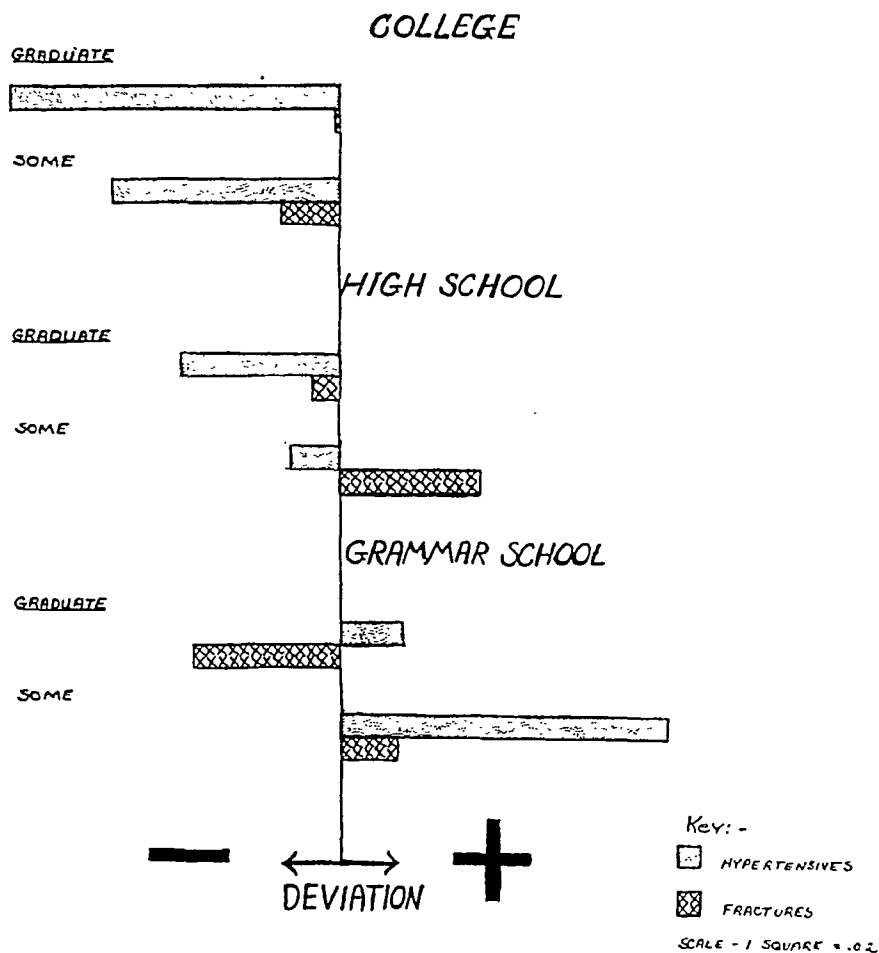


CHART 3. Educations.  
 Males—Females 21-55.  
 Base—Upper 60% General Population.

deviation from the upper 60 per cent of the population in the groups representing *incomplete* educational units (with the exception of the incomplete college group)\* and a minus deviation in the groups representing completed educational units. As will be seen from chart 3 this does not mean that accident patients have a lower educational average than patients with cardiovascular disease: patients with hypertensive cardiovascular disease as well as other groups studied fell much below them, although in our series patients

\* This minus deviation is probably to be explained in terms of the tendency of these patients not to go to college, plus other factors which in view of limitation of space cannot be discussed here.

# MUCOUS COLITIS: A DELINEATION OF THE SYNDROME WITH CERTAIN OBSERVATIONS ON ITS MECHANISM AND ON THE RÔLE OF EMOTIONAL TENSION AS A PRECIPITATING FACTOR \*

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Mucous colitis is a bodily reaction rather than a disease entity. In this it resembles such syndromes as asthma and epilepsy. Its manifestations are manifold and inconstant, often overshadowed by other symptoms, sometimes adeptly mimicking unrelated disease. The clinical picture is a hazy one at best, yet because of the very qualities which characterize it, its recognition is extremely important. Mucous colitis is probably responsible for the removal of more undiseased appendices than any other one cause. It is often mistreated, with resultant invalidism which may in some instances be avoided. It accompanies many of the states of emotional tension which are encountered in practice. Its apparently close physiological relation to such tension suggested to the authors the value of a clinical and psychological review of the syndrome.

DaCosta<sup>1</sup> was the first modern clinician to present adequately the syndrome of mucous colitis. In his paper is to be found an excellent list of references to the classical literature and to the early nineteenth century contributions. No attempt is made here to review in detail the history of the syndrome, but in many of the subsequent paragraphs reference is made to the significant work published since the appearance of DaCosta's article.

During a period of two years an attempt was made to study all the cases of mucous colitis which could be found in the wards or out-patient department of the Massachusetts General Hospital. In addition to cases obviously recognized as mucous colitis the authors attempted to interview briefly all patients with unexplained diarrhea, abdominal pain, or symptoms of the anxiety state. In this way certain patients were located who would otherwise have been overlooked. Many of the patients so interviewed, of course, showed no confirmatory evidence of mucous colitis and were disregarded. A total of 60 patients was studied clinically in sufficient detail to afford a basis for certain statistical deductions. Of these, 57 were studied in a psychological manner with sufficient thoroughness to afford considerable insight not only into the rôle of precipitating emotional factors but also into the types of personality encountered in the victims of the syndrome. The present report is concerned primarily with the clinical findings.

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From the Medical Clinic of the Massachusetts General Hospital and the Department of Medicine of the Harvard Medical School.

It may seem absurd to cite such illustrations as these but to any practicing physician who has heard almost the same stories from one patient after another over a period of 10 years and stories which differ so markedly from one group to another they begin to assume significance. It may be amusing

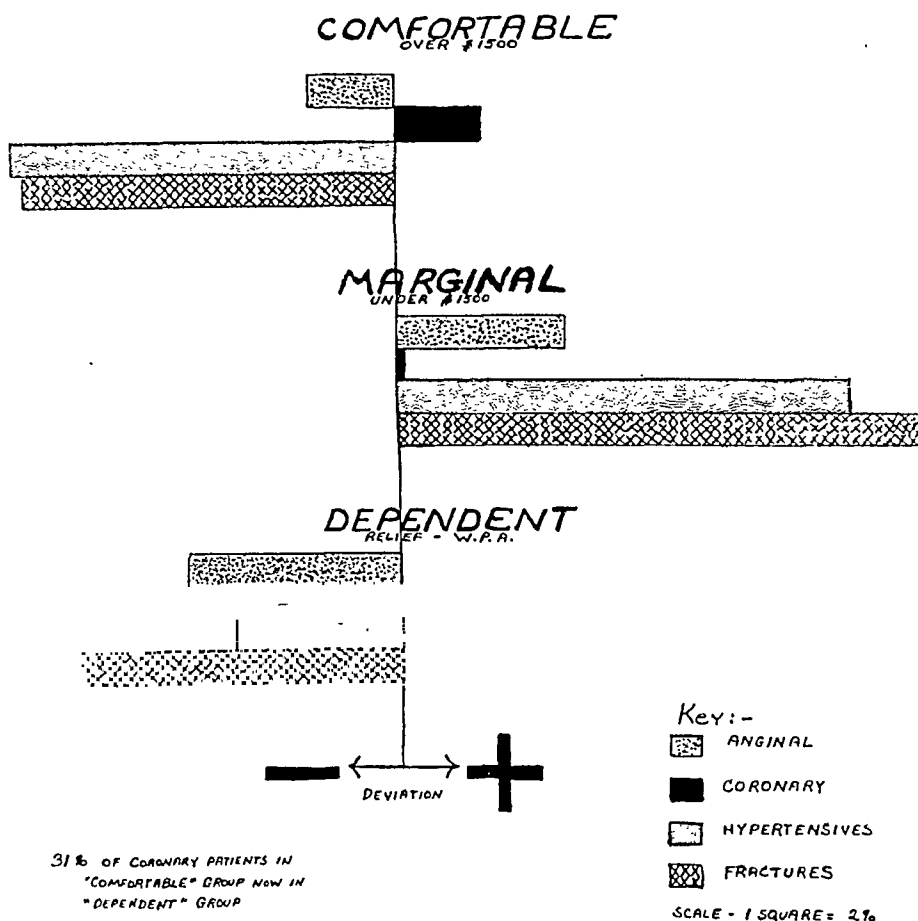


CHART 4. Incomes.  
Males—Females 21-55  
Base—General Population.

to note that when we first undertook this study although we were aware that a control group was out of the question and we could hope at best to study contrasts of one group with another, the fracture group was suggested to us as the most nearly normal group in the hospital because after all accidents happen by accident. At the time our study was undertaken, physicians under Health Insurance in Great Britain and Insurance Companies here were calling attention to the fact that only 10 to 15 per cent of accidents can be accounted for on the basis of defects in machinery, defects in skill, or physical or mental health of those involved. They were beginning to publish articles enquiring as to what this *x* factor in the personality was that predisposed certain persons and not others to accidents.<sup>2</sup>



In 38 instances the original diagnosis was other than "colitis." In some instances the original diagnoses were correct additional diagnoses, e.g. psychoneurosis, irritable heart, pregnancy, myxedema, asthma, allergy, diaphragmatic hernia, and peptic ulcer and Addison's disease each in one instance. All the remainder were frank errors. These aberrant diagnoses were for the most part suggested by one or another of the protean mani-

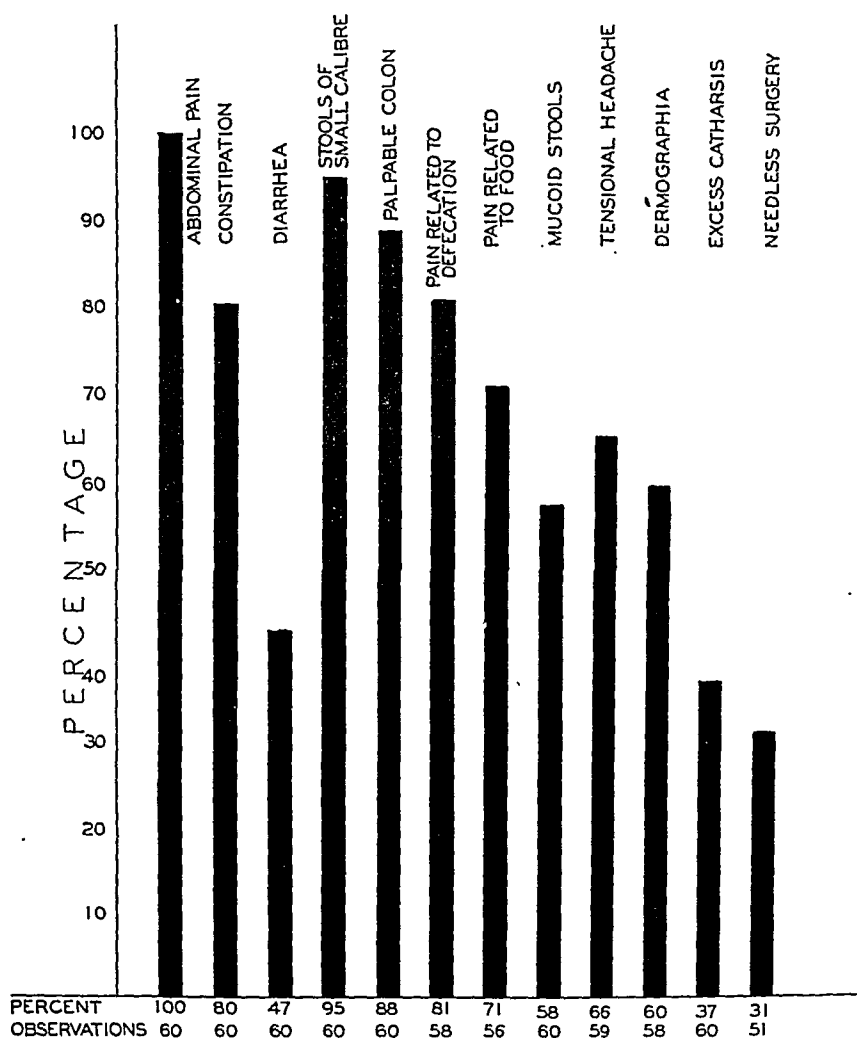


FIG. 1. Findings associated with mucous colitis. Abdominal pain is the most constant symptom, while constipation occurs almost twice as frequently as diarrhea.

festations of illness afforded by sufferers from mucous colitis, whether abdominal, cardiovascular, or neurasthenic in nature.

The frequency of the multiple symptoms and signs of mucous colitis is shown in figure 1. Eighty per cent of the patients had constipation at some time in the course of the illness whereas only 47 per cent had diarrhea. Indeed the majority of the patients with diarrhea gave a history of previous

A picture of the *illness history* prior to the development of the illness in question is perhaps the most interesting of all.

*First*, 72 per cent of the fracture patients had had one or more previous accidents.\* Fifty per cent of them had had two or more, the maximum being 27, whereas only 2 per cent of the patients in the other groups had had more than one accident.

*Second*, apart from their accident history, the fracture group had an illness record which is in marked contrast to that of the other groups and

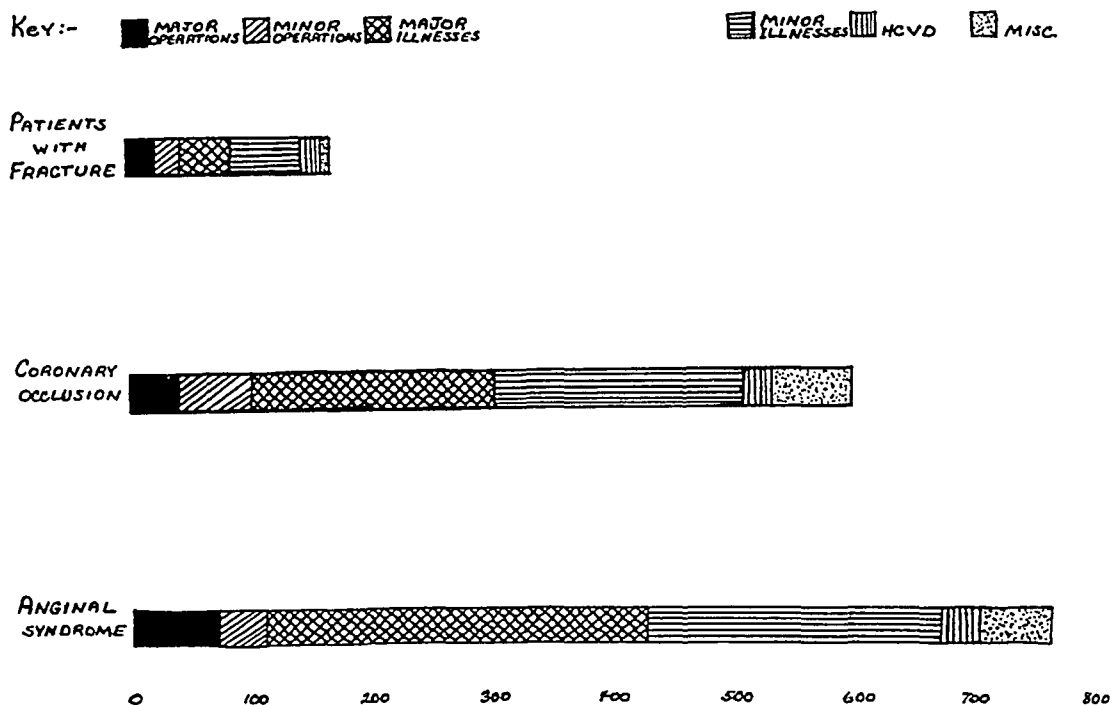


CHART 6. Illness incidence prior to present illness.  
(Corrected for age and sex distribution.)

much better than that for the general population (see chart 6). The total previous illness history (excluding accidents in all groups) for coronary and anginal patients was about five times as great as that for the fracture patients even after the figures had been corrected for age distribution. The majority of them represented disorders involving vegetative functions such for example as gastric or duodenal ulcer, acute appendicitis, gall-bladder disease, genitourinary dysfunction or pathology. (See chart 6.)

*And most interesting of all in spite of the points noted with regard to income and occupation, accidents represented only about 6 per cent of the illness history for the other two groups whereas they represented 76 per cent of the illness history of the fracture patients.*

It will remain for future study to determine whether or not our sample was adequate, and to evaluate the selective factor brought in by our par-

\* For fuller detail see references 3 and 4.

Lower abdominal pain was described as being "cramp-like" in 66 per cent of the cases. It was described as a sensation of pressure or of "gas" in 30 per cent, and was described as being sharp in 13 per cent. Some patients employed more than one term in describing it. "Cramps," "pressure," and "gas" were described with equal frequency in the upper abdomen, whereas sharp upper abdominal pain was described in only 10 per cent of the cases. Occasionally a patient complained of a burning sensation, commonly referred to in the literature as "pyrosis coli," and at times patients described granular sensations as if two pieces of sandpaper were rubbing together.

The physical findings in mucous colitis are few. The only statistically tabulated finding pertinent to the syndrome itself is palpability of the colon. The colon was found to be palpable in 91 per cent of the cases. In most cases the sigmoid was palpable as a firm contracted "rubber hose" while the cecum was often found to be distended and tender. The other physical findings frequently encountered were those of the anxiety state: widely dilated pupils, tachycardia, excessive sweating, cold, moist hands, hyperreflexia, taut muscles in the back of the neck, flushing of the neck and chest, tremor of the hands, etc. An excessive red response to stroking of the skin was encountered in 60 per cent of the cases.

There are no specific diagnostic laboratory procedures. The sigmoidoscope, however, does reveal changes which are definite and are suggestive of the condition. Such changes were found in 89 per cent of the patients in this series. According to Friedenwald, Feldman, and Rosenthal<sup>5</sup> the development of the sigmoidoscopic picture may be divided into three phases:

*Stage 1.* Vessels engorged with dilation of mucosal capillaries. Mucous membrane covered with glairy mucus. Slight granularity lending "shad roe" appearance.

*Stage 2.* Generalized injection against which vessels no longer stand out clearly. Surface drier with no glare. Disappearance of light reflex. Mucus dry and tenuous, appearing in patches on mucosal surface.

*Stage 3.* Mucous membrane thinned out, pale, covered with mucus. Pin point ulcerations on removal of surface mucus.

A moderate amount of spasm may be present in any of the three stages. These changes are not specific for mucous colitis. They may be present in the normal colon after irritant enemata, in the course of infectious enteritides, or in diseases in which there is irritation in proximal portions of the colon, e.g. proximal ulcerative colitis, diverticulitis, carcinoma, etc. There are also a few patients with the earlier manifestations of mucous colitis in whom no changes are observable. Our experience and that of two other groups of workers<sup>5,7</sup> are in close agreement as to the value of the sigmoidoscopic examination (table 2). Although in this study no attempt was made carefully to delineate the three stages, the findings were closely in agreement with those of Friedenwald, Feldman, and Rosenthal.

Finally, we have added a little more factual background to the old medical axiom—"it is more important to know what kind of patient has a disease than what kind of disease a patient has."

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TABLE II

Incidence of Clinical Findings as Reported by Four Groups of Workers. There is general agreement as to the sexual incidence, the frequency of abdominal pain and of associated upper abdominal symptoms. There is close agreement as to the frequency of constipation and as to the value of sigmoidoscopic examination. There is more divergence of opinion as to the occurrence of diarrhea and regarding the value of examination by roentgen-ray.

	This Study	Friedenwald, Feldman, and Rosenthal	Bockus, Bank, and Wilkinson	Jordan and Kiefer
Upper abdominal pain or dyspeptic symptoms.....	48%	64%	58%	59%
Abdominal pain.....	100%	93%	70%	90%
Constipation.....	80%	72%	80%	80%
Diarrhea.....	47%	19%	44%	9%
Males.....	27%	16%	36%	23%
Females.....	73%	84%	64%	77%
Sigmoidoscopic changes.....	89%	89%	92%	—
Spasm by roentgen-ray.....	18%	51%	43%	27%
Food allergy.....	3.3%	1%	—	—
Coincident peptic ulcer.....	6.7%	8%	4%	—
Average age.....	36	30	36	30

There is some confusion in terminology with reference to the mucous colitis syndrome. Most clinicians fail to diagnose those forms in which diarrhea is not the predominating symptom. Hence the majority of medical men are taught to employ the term only in referring to the relatively small group in which intractable chronic mucous diarrhea is the primary finding. That this limited group fails to represent many cases with symptoms due to abnormal function of the colon is apparent. Jordan and Kiefer use the term "irritable colon" to include a very wide range of intestinal complaints, even to the point of making that diagnosis in 33 per cent of the patients seen in their gastrointestinal clinic. We have chosen a middle course and employ the term "mucous colitis" more broadly than is done by the average clinician. Yet we restrict it to those patients in whom there is good clinical evidence of colonic involvement. That there is not too wide a discrepancy in the minds of workers in the field is attested by table 2 in which the findings obtained in four moderately extensive surveys are shown in parallel columns. Note that Jordan and Kiefer found diarrhea in only 9 per cent of their cases indicating the wider range of patients included in their series. In all four series, however, the incidence of upper abdominal symptoms, abdominal pain, etc. are comparable. Sigmoidoscopic changes were noted in almost exactly the same percentage of cases in the series in which such observations were made.

## II. MECHANISM

Hypotheses as to the etiology of mucous colitis are inextricably bound up with the history of the disease. DaCosta described in 1871 seven cases of severe mucous colic. He was conversant with the cases of diarrhea suffered by the soldiers during the American Civil War and recorded by Woodward.<sup>12</sup> DaCosta observed the similarity between them and the patients in his series.

## I. CLINICAL SYNDROME

In general the symptoms and signs of mucous colitis are constipation or diarrhea with mushy or pebbly stools of small calibre, abdominal cramps aggravated during peristaltic stimulation, palpable and tender sigmoid colon, and certain minimal mucosal changes in the rectosigmoid as observed through the sigmoidoscope. In the present series abdominal pain was the only constant finding. The authors do not deny the real probability that mucous colitis may exist in the absence of a history of abdominal pain, and a few such cases may have been overlooked. Abdominal pain, whether sharp, cramp-like, or present as a sensation of pressure or "gas," is so common, however, that its presence was considered the one constant finding in the syndrome.

In view of previous clinical observations on the inconstancy of constipation and diarrhea, the variability in the type of stools, the manifold locations and types of abdominal pain, the frequent occurrence of upper gastrointestinal disturbances, the association of cardiovascular symptoms, the frequently reported significance of allergic factors, and the possible rôle of excess catharsis as an etiological factor, a master chart was prepared incorporating these and other data considered to be significant. Statistical conclusions drawn from that chart are reported herewith. Most of the data were completed for every patient and percentages in most instances are based on the study of that number. In a few instances some data are missing for a small number of cases, but all percentages are based on the study of at least fifty-four.

TABLE I

Initial Diagnoses on First Admission to Hospital. Note the multiplicity of conditions with which mucous colitis may be confused. The eight unlisted diagnoses were correct but unrelated.

Diagnosis	No.	Per Cent
Colitis.....	22	37.0
Psychoneurosis.....	17	28.0
Gall-bladder disease.....	3	5.0
Appendicitis.....	2	3.3
Peptic ulcer.....	2	3.3
Cancer of stomach.....	2	3.3
Irritable heart.....	2	3.3
Addison's disease.....	2	3.3
All others.....	8	13.3

Mucous colitis is a disease whose onset usually occurs in early adult life. The average age of onset of symptoms was 23.4 years. Two cases developed before the age of 10, seventeen cases between 10 and 20, twenty-six cases between 20 and 30, eleven cases between 30 and 40, while only four cases developed after the fortieth year. The average age at the time of this study was 35.8 years, indicating a fairly long average prediagnostic period. The initial diagnoses of the patients in this series are enumerated in table 1.

histologically normal colons in persons who had suffered from severe "colica mucosa" attacks. Nothnagel realized that cramps and mucoid stools could occur in the presence or absence of focal lesions, and he divided his cases accordingly. Westphalen<sup>24</sup> attempted to reconcile these views by formulating the arm-chair concept that all excess mucous secretion was due to nervous impulses, which however, in the infectious enteritides were secondary to inflammation.

In the years following this controversy no one has succeeded in isolating an infectious organism, while further evidence as to the unstable nervous systems of the sufferers has been advanced. DeLangenhagen<sup>25</sup> in 1903 reported a series of 1200 cases, all of which he described as being neurotic. He emphasized manifestations of vascular instability, and he commented on the frequency with which symptoms of severe anxiety were encountered. Subsequent European contributions were largely radiological in nature, throwing light on the disturbed motility of the colon discussed elsewhere. At the end of the First World War Hurst,<sup>26</sup> as Woodward and DaCosta had done before, pointed out the frequency of diarrhea among the soldiers and the frequent coexistence of diarrhea and cardiovascular instability.

After that war interest in the mucous colitis syndrome again returned to this country. Allergy as an etiological factor in a small number of cases was established by Duke<sup>27</sup> and Hollander.<sup>28</sup> Attempts at establishing an allergic disturbance as the cause of a larger number were also made<sup>29</sup> and the rôle of bacterial allergy was investigated.<sup>30</sup>

Less immediately related to the clinical syndrome of mucous colitis the whole field of the autonomic nervous system was tilled, light was thrown upon the chemical mediation of nerve impulses, and on the central representations of the autonomic nervous system. Experimental surgery, clinical observation of neurosurgical patients, and pharmacological studies confirmed adequately this last relation. The work of Cannon and Britten,<sup>31</sup> Bard,<sup>32</sup> Cushing,<sup>33</sup> Light, Bishop, and Kendall,<sup>34</sup> and Keller, Hare and d'Amour<sup>35</sup> is of pioneer significance. In the light of this background further evidence is accumulating which supports the belief that mucous colitis is a secretory and motor neurosis of the intestine.

White and Jones<sup>36</sup> succeeded in producing mucosal changes in many respects similar to those seen in mucous colitis by the topical application of pilocarpine and of physostigmine within the rectosigmoid. Pilocarpine was found to have an almost immediate effect in producing glairy mucous secretion, diffuse injection, wrinkling of the mucosa, and constant spasm with a squirming movement of the intestinal wall. The changes were maximal five minutes after application. Physostigmine was found to produce its effect more slowly. After five minutes the mucosa was seen to be pale and swollen, presumably due to the presence of edema. At the end of 15 minutes' time, however, mucous secretion, wrinkling of the mucosa into coarse folds, and spasm were constantly observed. The difference in time interval is presumably due to the different modes of action of the two drugs, pilocarpine

constipation of the type characteristic of mucous colitis. In many instances patients with infrequent small mushy movements were unable to decide which appellation to employ. Patients with this type of constipation complain as a rule not of large, hard, painful dejections, but rather of an absence of any urge to defecate. Their movements, when they occur, are either composed of multiple hard, dark, spheroidal "rabbit pellets" or else are small, mushy, and described as "the size of a pencil." This type of constipation is aggravated by high cellulose diets, over-exercise, and cathartics, is relieved by low residue foods, relaxation, and atropine derivatives. There is evidence that it is due in part to spasm of the descending colon, sometimes with cecal retention and that it corresponds with Stierlin's<sup>2</sup> "constipation of the ascending type" and Fleiner's<sup>3</sup> "spastic constipation." The authors believe, on the basis of data presented elsewhere, that this type of constipation and mucous diarrhea are manifestations of the same bodily dysfunction, the former generally preceding and being milder than the latter. Mallory<sup>4</sup> suggested that spastic constipation, mucous colitis, and ulcerative colitis might represent progressive stages in the same process. Inasmuch as no patient in this series developed ulcerative colitis under observation, and inasmuch as many cases of ulcerative colitis begin suddenly without antecedent spastic constipation or mucous diarrhea, Mallory's supposition cannot be confirmed on the basis of this study. The types of stools encountered in patients with constipation and with diarrhea are shown in figure 2. It will be noted that even in the constipated group of patients small mushy movements are encountered with greater frequency than any other type.

Certain factors tending to precipitate pain are recorded in figure 1. To these factors must be added others which predispose to it in a more general way. Such factors are physical exhaustion, athletic "softness," fatigue, infection, emotional tension, and the like. The significance of such factors is discussed below. The locations at which pain was most frequently encountered are illustrated in figures 1 and 3. The most common single location was the left lower quadrant, where pain was found in 78 per cent of the cases. Lower abdominal pain occurred in 95 per cent, while discomfort was limited to the upper abdomen in only 5 per cent. Pain occurred more frequently at multiple sites than in one location alone. When limited to one location the left lower quadrant was most commonly involved, the upper abdomen and right lower quadrant being much less frequently the site of discomfort.

From figure 1 it is apparent that pain occurred following the ingestion of food in 71 per cent of the cases. In some cases this served as a differential diagnostic point from peptic ulcer, in which food relieves the abdominal pain. The aggravation of pain following the ingestion of food is presumably due to stimulation of the gastrocolic reflex. In about 80 per cent of the cases there is a definite association between the desire for defecation or the act of defecation and periods of aggravation of abdominal pain. This, again, is supposedly the result of colonic activity.



often were suppressed and gave way to violent explosive movements. Katsch found the maximal change after pilocarpine to occur in 12 minutes after injection, while the maximal change after physostigmine did not occur for 30 minutes. Atropine was found to diminish tonus and movement, while adrenalin produced complete cessation of movement.

The evidence for the production of colonic changes similar to those seen in mucous colitis by stimulation of the parasympathetic nerve endings is essentially complete. What is lacking is evidence that innervation of the bowel via parasympathetic nerve fibers will produce these changes. Unfortunately the pelvic nerve is so filamentous that it does not lend itself to direct stimulation either in man or in laboratory animals. Studies by Banting and Hall<sup>38</sup> and by Manning, Hall and Banting<sup>39</sup> show that mucosal lesions of the stomach and upper intestinal tract result not only from prolonged intravenous administration of acetylcholine but also from prolonged direct vagus stimulation. These experiments suggest that stimulation of the sacral division of the parasympathetic nervous system, if practicable, should also produce mucosal changes in the bowel.

A number of conditioning factors seem to play a rôle in the production of symptoms in mucous colitis. Among these are direct irritants of the colon, such as rough foods, cathartics, enemata, and coincidental colonic infections such as acute enteritis, or amebic or bacillary dysentery. Factors which produce instability of the autonomic nervous system are also important. These include general infectious diseases, particularly influenza and "grippe," sudden weight loss, and physical "softness." White, Cobb, and Jones<sup>40</sup> showed that patients with mucous colitis had extremely low physical efficiency scores both in terms of the Schneider<sup>41</sup> and Turner<sup>42</sup> tests. These are tests of cardiovascular stability which correlate moderately well with athletic fitness. Specific food allergy is a factor which appears to be important in a small number of cases.

Many investigators<sup>1, 13, 14, 15, 25, 7, 40</sup> have shown emotional factors to be extremely important. There is evidence that in the given individual symptoms may occur only when a number of these factors are concurrently present.

### III. RÔLE OF EMOTIONAL TENSION

Sixty cases of mucous colitis were reviewed clinically. Of these, 57 were studied psychologically in sufficient detail to justify certain conclusions regarding the personalities of the sufferers and the rôle of emotional tension in precipitating the symptoms. These 57 cases were divided into two groups, a more neurotic group handicapped by psychoneurotic symptoms or by personality problems, and a less neurotic group composed of persons whose personality problems were not incapacitating. The severity of mucous colitis symptoms was not used as a criterion for this line of demarcation. An attempt was then made to determine in which patients exacerbations of symptoms occurred in association with readily understandable causes for

In contrast with direct sigmoidoscopic observation, the routine barium enema is of comparatively little value from a diagnostic standpoint. In the present series spasm was seen in only 18 per cent of the cases which were so examined. Yet Friedenwald, Feldman, and Rosenthal found spasm to be the most common roentgen-ray finding. In their series it occurred in 51 per cent of the cases. Jordan and Kiefer<sup>6</sup> found spasm in 27 per cent and Bockus, Bank, and Wilkinson<sup>7</sup> in 43 per cent. Despite their lack of diagnostic value, the changes observed by roentgen-ray methods are of interest in explaining the disturbed physiology which characterizes this disease. The observation of the head of the barium column after oral ingestion is said by Kantor<sup>8</sup> to yield the most significant results. By this technic one may see that the barium column travels faster than is normally the case, the head of the column often reaching the splenic flexure in six hours instead of nine. The distal portion of the colon is often "pulled out" with flattening of the haustrations and spasm and may contain flakes or streaks of barium. At times these assume a stringy or ropy appearance, which Crane<sup>9</sup> has called the "string sign." It was originally described by Schwartz.<sup>10</sup> Information may also be obtained from carefully administered non-irritating enemata after preparation of the colon with saline irrigations. The barium must be introduced slowly and at a pressure not greater than 30 inches of water. Under these conditions, as Kantor points out, the colon is seen to fill more rapidly than normally, and the filling is accompanied by abnormally severe pain. The amount of fluid required to fill the colon is found to be only 32 ounces instead of the 36 to 40 ounces usually required. Spasm and flattening of the haustra of the descending colon are also frequently observed. Sometimes the pulled-out appearance of the descending colon is described as redundancy. Often there are abnormally deep haustrations in the transverse colon. Schwartz showed that in some cases the irritability was so great that mass spasm of the descending colon could be observed. Schatski<sup>11</sup> in studying one of the cases in the present series under controlled conditions was able to confirm the widely accepted observations described above. In addition pressure over the left side of the abdomen produced mass spasm of the descending colon and relaxation of the transverse colon while pressure over the midepigastrium produced spasm of the transverse colon and relaxation of the descending colon. All these changes are of physiological importance, but in view of the uncontrolled conditions under which routine roentgen-rays are made, the evaluation of such changes is extremely difficult. Furthermore, inasmuch as spasm is a transient state, it may at the time of any given examination fail to be seen (table 2).

Blood and urine studies in mucous colitis are normal. Eosinophilia, which might be expected because of the similarity of the disease to bronchial asthma, is usually absent. The stools are not remarkable except as to size, shape, color, consistency, and the presence or absence of mucus. The types of stools seen in patients with constipation and with diarrhea respectively are shown in figure 2 and are discussed elsewhere.

cent of the cases, is consistent with prolonged dwelling upon problems and hence abnormal continuation of resentment, guilt, anxiety, or other mental states.

An adequate review of psychiatric case histories is beyond the scope of this article. The following two summaries, however, show the type of

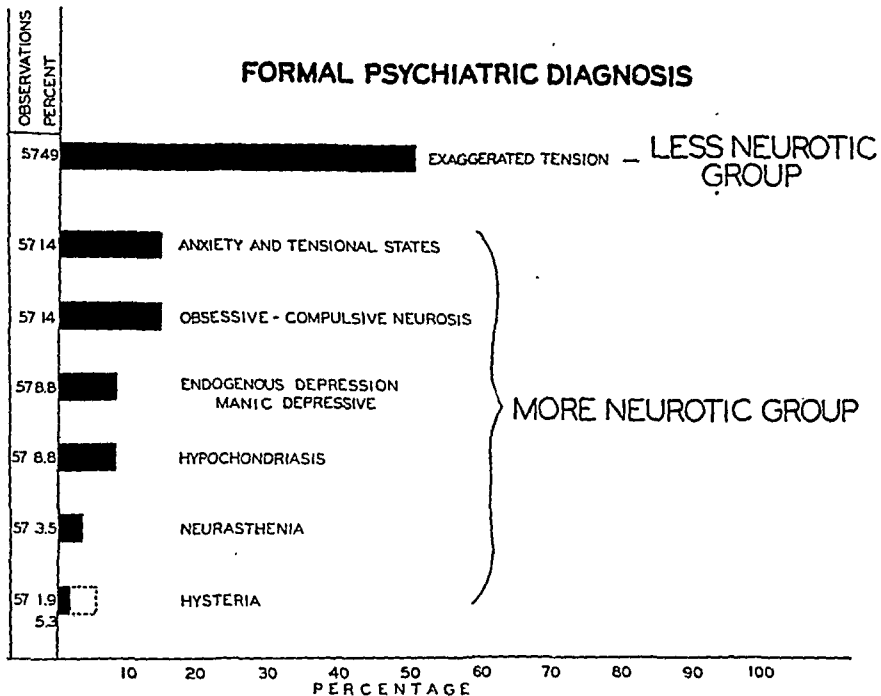


FIG. 4. Formal psychiatric diagnoses. There is no one diagnostic classification even for the patients in the more neurotic group. Note that hysteria (dissociative and dysmnesic state) is least frequently encountered.

reaction often encountered in less neurotic and more neurotic cases respectively. These two cases are chosen because their problems lend themselves to brief presentation.

*Case 1.* A 22-year-old, native born welder appeared in the medical clinic for the first time on October 16, 1936.

Chief Complaint: Constipation and epigastric pain of 10 months' duration.

Family History and Past Medical History: Essentially negative.

Present Illness: In January 1936 the patient first began suffering from constipation. He had one pebbly bowel movement every five days. He also developed epigastric pain, aggravated by meals, relieved by belching. This pain showed no relation to bowel movements, was not relieved by food. It became most severe in June 1936, and persisted in a discommoding degree until the time of admission to the clinic. On questioning, the patient said that he had definite cramp-like pains in both lower quadrants of the abdomen which were aggravated in association with defecation.

Physical Examination: The patient was a slightly built asthenic man with no gross physical abnormalities. His pulse was labile, and his colon was palpable and tender.

He described the clinical syndrome with accuracy, noting the frequency of abdominal pain, of dyspepsia, and, surprisingly, of associated mucous discharge from the uterine cervix. He studied the rectal mucosa through a speculum and described its angry red and thickened, but non-ulcerated, ap-

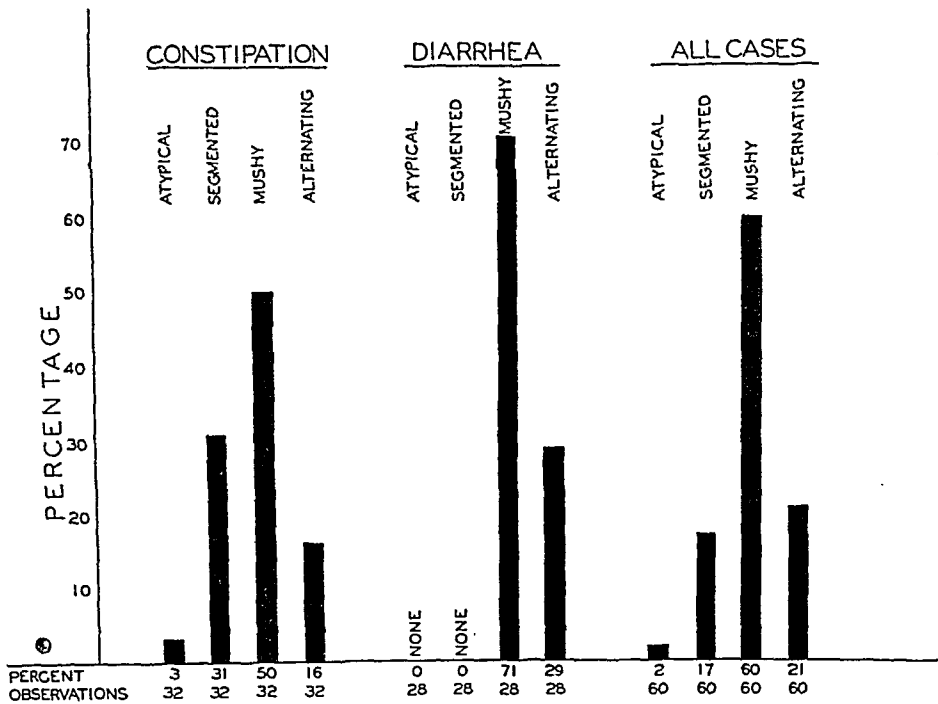


FIG. 2. Types of stools in mucous colitis. All stools are small in calibre except those listed as atypical. Mushy stools occur most frequently even in the patients suffering only from constipation. Small segmented pellets occur only in that group.

pearance. He recognized the tense, emotionally unstable nature of the patients, and he concluded that the disease was a manifestation of nervous tension and physical disability. In his original paper are numerous references to the classical authors who were aware of the rôle of emotion in the production of diarrhea. To DaCosta belongs the credit for elevating "Membranous Enteritis" to the dignity of a syndrome. After DaCosta's contribution great interest in the syndrome developed in Europe. The earlier European writers, Nothnagel,<sup>13</sup> Marchand,<sup>14</sup> and vonLeube<sup>15</sup> emphasized the concept that the disease was really a secretory and motor neurosis of the intestine, while their immediate followers, Einhorn,<sup>16</sup> Boas,<sup>17</sup> Ebstein,<sup>18</sup> and Schutz<sup>19</sup> disagreed to a certain extent with this simple concept. All the latter workers tended, rather, to emphasize the rôle of inflammatory processes in the colon, a view which among contemporary writers is exemplified by Niles.<sup>20</sup> VonNoorden<sup>21</sup> in reviewing the evidence for these two beliefs, emphasized the fact that paroxysmal attacks of pain with mucous diarrhea were at times observed in patients with infectious enteritides, but he was impressed by Rothmann's<sup>22</sup> and Hemmeter's<sup>23</sup> findings at the autopsy table of

The only aggravation in symptoms after the patient came under observation in October 1936, was when he became involved in a minor automobile accident which involved some litigation. During a period of a few days following the accident he had a recurrence of symptoms.

Case 2. A 35-year-old, native born spinster entered the hospital January 12, 1938.

Chief Complaint: Constipation of ten years' duration.

Family History: Essentially not remarkable.

Past Medical History: The patient had had in addition to the usual childhood diseases scarlet fever, diphtheria, influenza, herpes zoster, and pneumonia. She had had her appendix removed at the onset of the acute phase of her present illness. She had always suffered from easy fatigability, occasional palpitation, and headaches.

Present Illness: The patient was well until 10 years before admission to the hospital at which time she began to suffer from chronic constipation for which she began the occasional use of cathartics. Her illness was not severe, however, until 1935, at the age of 33, when it became grossly severe and was accompanied by cramp-like pain in the right lower quadrant of the abdomen. The pain was aggravated following the ingestion of meals, particularly those composed of rough foods, and was noticeably increased at times of emotional upsets. Her stools were hard, small, and composed of pellets. In addition to the increased severity of her constipation, at the time of admission she was developing upper abdominal symptoms, including epigastric distress, belching, sour eructations, heartburn, coated tongue, and bad breath, about which she was also concerned. In addition she developed almost constant nagging occipital headache, accompanied by tension of the posterior neck muscles and aching in the right trapezius region. All these symptoms remained unabated until her admission.

Physical Examination: The patient was a well developed and nourished, neatly dressed woman whose gestures were distinctly mechanical. Her descending colon was palpable and tender. She showed excessive sweating. Her tendon reflexes were hyperactive, but she had no tremor.

Special Data: A sigmoidoscopic examination revealed definite irritability of the rectosigmoid with some reduction in calibre. The mucosa was distinctly injected, and there was much glairy mucus present. The veins were prominently distended, standing out from the mucosal background.

Psychiatric Observations: The patient's father, the proprietor of a small butcher shop, had settled in a small city 10 years before the patient was born. Her mother was the disciplinarian of the family, and throughout the patient's life had been a thorn in her side. In school the patient had done well both academically and socially and had planned to go to the state normal school. This was impossible because of her father's circumstances, and because there was no local normal school in her native city. She felt bitterly about her inability to obtain this added education and bore overwhelming resentment against her parents: (a) because they could not understand her position in feeling that she needed this education, (b) because she felt that they might have been able to afford it had they made other sacrifices, and (c) because they had been so stupid as to settle in a manufacturing city when they might have settled in a city which boasted a normal school. Therefore, at the age of 19 she moved to another city and worked in an office. When she was 22, however, she returned home to nurse her ailing mother, and spent six miserable years at the task before her mother finally died. During this time she did take an evening course in beauty culture and after her mother's death spent some years working as a "beautician."

In 1935, at the age of 33, her most acute state of emotional turmoil developed. She went to a large city to take a short course in hairdressing. While there she consulted a young physician professionally. He was sympathetic and developed a real interest in her. She saw him on numerous occasions, felt that marriage to him was

being a direct stimulant to parasympathetic activity, physostigmine merely serving to inhibit the action of cholinesterase upon the normally produced acetylcholine at the nerve endings. White and Jones also observed diffuse

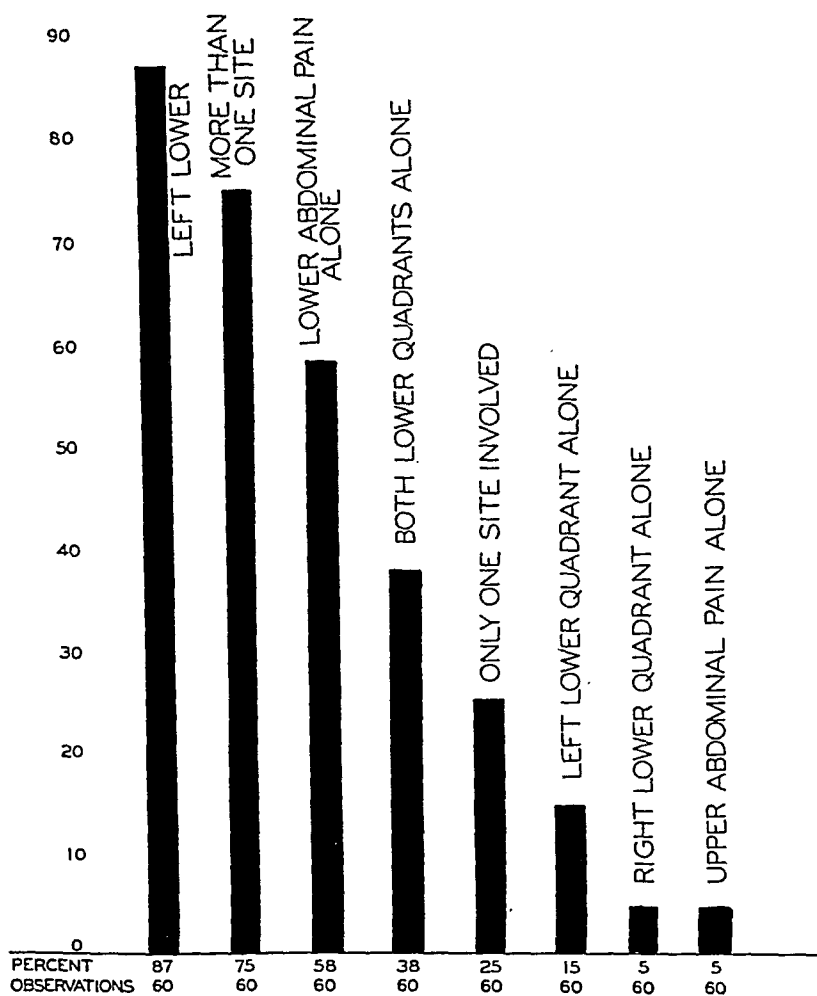


FIG. 3. Most frequent sites of abdominal pain. The left lower quadrant is almost invariably involved. Note that upper abdominal pain alone occurs in only 5 per cent of the cases.

changes in the rectal mucosa after the administration of large doses of acetyl-beta-methyl choline and of carbaminoylcholine by mouth. The mucosal changes produced in this way were almost identical with those described by Friedenwald, Feldman, and Rosenthal in the second stage of mucous colitis, i.e. diffuse injection with obliteration of venular markings, fine wrinkling of the mucosal surface, dull tenuous mucoid secretion, and inconstant spasm. Katsch<sup>37</sup> had previously demonstrated by observing roentgenologically the barium filled colon that pilocarpine and physostigmine produced increased depth of haustra in the transverse colon and areas of spasm and of increased motility in various portions of the colon. The small normal movements

## SUMMARY

The syndrome of mucous colitis is sufficiently clear for accurate diagnosis in the majority of cases. The diagnosis is applicable to a greater number of persons than are included in this group by the average clinician. "Mucous colitis" comprises a narrower group than is included by the term "irritable colon" as employed by Jordan and Kiefer. In general patients with mucous colitis suffer from constipation or diarrhea with some form of abdominal pain. In most cases the stools are small and are either mushy or composed of hard pellets. As a rule the symptoms are seen in persons who have labile autonomic nervous systems with concurrent cardiovascular instability, and are most pronounced in persons who are in poor athletic training. The lower abdominal pain is generally accompanied by upper abdominal symptoms such as nausea, heartburn, belching, and sour eructations. Cardiovascular symptoms such as palpitation, sweating, faintness, and neurocirculatory asthenia are often encountered. On physical examination the sigmoid colon is often palpable as a firm "rubber hose." The stigmata of instability of the autonomic nervous system, flushing, sweating, cold, moist hands, instability of the pulse rate, dilatation of the pupils, and abnormally red skin response to scratching, are frequently encountered. Instability of the cardiovascular system is further evidenced by so-called physical efficiency tests. The signs and symptoms, therefore, appear to be essentially those frequently noted in somatic neuroses such as neurasthenia and anxiety states.

Evidence is presented that changes in the rectosigmoidal mucosa similar to those seen in mucous colitis may be produced by the topical application of drugs which stimulate or simulate the action of the parasympathetic division of the autonomic nervous system. In some instances these changes may be produced by the oral administration of such drugs.

Certain observations on the frequency of psychogenic factors as precipitating agents in mucous colitis are also presented. In most instances mucous colitis appears to be a somatic response to a type of nervous tension. Mental states conducive to this response appear to be those of anxiety, resentment, and guilt. Associated depressive, neurasthenic, and hypochondriacal features are often present, but no one psychiatric diagnosis comprises the mucous colitis group. A rigid type of thinking, similar to that seen in obsessive-compulsive states, is present in 50 per cent of the cases and may play a rôle in prolonging periods of tension. The symptoms of mucous colitis appear to represent a clear-cut somatic response to tension and not to be psychologically determined and obviously gainful such as those seen in hysteria.

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emotional tension. It was found that in four of the patients in the less neurotic group there was no relation between emotional tension and the development of symptoms. Two of these cases had their colonic symptoms in association with hives, and there is other evidence that they were allergic. A third patient had residual symptoms after emetine treatment for *E. histolytica*, and the fourth presented symptoms and chemical changes strongly suggestive of Addison's disease. With these four exceptions all the 28 less neurotic patients showed a close relation between emotion and aggravation of symptoms. In the more neurotic group there were 29 patients. Of these only 17, or 58 per cent, showed a close relation between emotion and colonic symptoms. The discrepancy between the two groups is probably to be explained on the basis of the complicated chains of psychological processes in more neurotic persons, most of which are unconscious in nature. The subjective importance of any given stimulus may be greatly increased or decreased by these "long-circuiting" processes. The disapproval of a parent may be grossly accentuated, the loss of a fortune minimized. Hence it is difficult for the psychological observer to evaluate the tension producing quality of various experiences.

An attempt was made to classify the patients on the basis of conventional psychiatric diagnosis. On this basis no common denominator could be found. The less neurotic patients with psychogenic symptoms were all found to be suffering from a normal or exaggerated normal tensional response. They could be labeled as tensional states. Anxiety states and tensional states accounted for 14 per cent of the more neurotic patients, making a total of 63 per cent of the psychogenic cases. The remaining 37 per cent were fairly evenly divided among obsessive-compulsive states, depressive states allied to the manic-depressive group, hypochondriasis, and neurasthenia. There was only one primary psychiatric diagnosis of hysteria (1.7 per cent) and there were two more patients in whom hysterical tendencies or malingering were present (figure 4).

Although no one diagnostic label could be applied to all the cases, nevertheless there were certain personality characteristics and psychiatric symptoms which occurred with great regularity. From figure 5 it is apparent that tension was present in 96 per cent of the cases and anxiety in 82 per cent. Resentment was present in 92 per cent and guilt in 67 per cent. Depression, dependence upon others, asthenia, and rigidity of thought were also frequently encountered.

Flynn<sup>43</sup> called to the authors' attention his original observation that the inhibition of retaliation in a state of anger led to a confused response of the autonomic nervous system in which parasympathetic reaction was predominant. The mental state associated with inhibited anger is resentment. That resentment was so frequently encountered in this series is of interest in the light of Flynn's observations. Guilt, which was also frequently observed, is a sort of inward resentment directed against one's self. The quality of rigidity or inflexibility of thought, which was noted in 51 per



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**Special Observations:** Gastrointestinal roentgen-ray examination revealed no abnormality of the esophagus, stomach, or duodenum. Sigmoidoscopic examination showed no abnormality within the rectosigmoid.

**Psychiatric Observations:** The patient had a congenial and friendly father, but his mother was a strict and domineering woman with fixed and rigid ideas. He lived in moderate suburban circumstances with his parents and a sister. He had had a high school education, one year of business training, and had been employed as a welder for three years. When he was eighteen years of age he had met a Protestant girl and introduced her to his mother, who heartily approved of her. He became engaged to the girl, saw her every few months, and wrote to her several times a week.

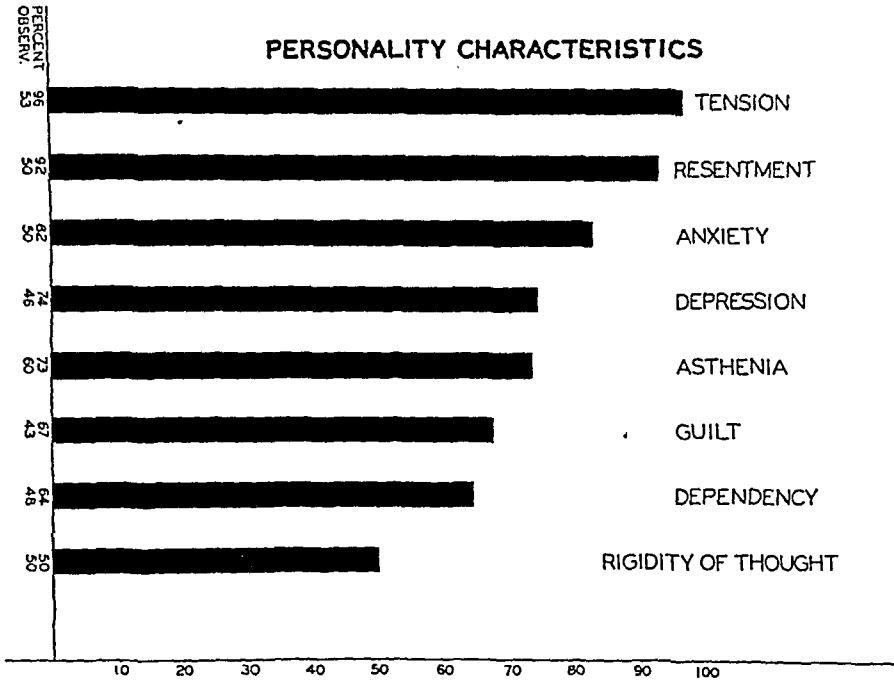


FIG. 5. Personality characteristics of patients with *mucous colitis*. Tension is the common denominator present in almost the entire group. The rôle of other factors in maintaining tension is discussed in the text.

In December 1935 he decided that he was no longer sexually attracted to the girl and that the time had come to break his engagement. He *did so against the* loudly voiced objections of his mother in January 1936, the very month of the onset of his symptoms. Immediately thereafter he began to devote his attentions to a young Catholic girl. This was entirely unacceptable to his mother, who was a Methodist. The tension grew more heated, and in June 1936, resulted in the patient's leaving home for the summer. This was the time at which symptoms were most severe.

**Course:** The patient's symptoms were instantly relieved by the use of atropine derivatives and a low residue diet. He was reassured to learn that his symptoms were not those of a peptic ulcer and was quick to realize the significance of the tension which had developed with his mother. He developed a policy of continuing his attention to the Catholic girl, which his mother soon found she was unable to thwart. On the contrary she developed an affection for the girl and accepted the situation gracefully. In May 1937, the pair were married, settled eight miles from home, and enjoyed emotional and physical happiness. Symptoms continued to remain in abatement.

found that only slightly more than 10 per cent of the school children of a rural community had been infected with tubercle bacilli. These observations may be looked upon as great landmarks of progress and of advancement of our knowledge of tuberculosis, for they were the beginning of a new era in the study of this disease. They so informed, inspired, and encouraged, that workers everywhere took heart. Ever since Slater reported his work the tuberculosis control program has rapidly increased in intensity and accomplishment. Large tuberculin testing programs were instituted, and it again became perfectly obvious that tuberculosis is contagious, when the workers administered tests and found that nearly all who were in direct contact with persons in the consumptive stage of tuberculosis became reactors. This stimulated efforts for the provision of places to isolate tuberculous patients in order to break or prevent contact between them and the uninfected. This was accomplished to such a degree that in many places the majority of girls and boys grew to adulthood without having been contaminated with tubercle bacilli. A problem as old as the disease itself now could be definitely proved to exist, namely, the spread of tuberculosis from the patients who had been isolated in institutions to protect their families and communities to those who cared for them in these institutions, particularly the nurses, both students and graduates. Wherever the tuberculin test was administered to students of nursing on entrance, during, and at the end of their course, a marked increase in the number of reactors was found to occur during training. In fact, in some places where only 30 to 50 per cent of the entering students reacted to tuberculin a full 100 per cent reacted before graduation, as reported by such authors as Heimbeck and Geer.

Boynton made observations on students in a school of nursing and students in a college of education. She found that "the tuberculosis infection rate is one hundred times greater in the student nurses on a general hospital service than in students in the college of education and five hundred times greater in student nurses on a special tuberculosis service than in college of education students."

Amberson and Riggins tested 539 student nurses and found that 57.9 per cent were reactors on admission. Of a group of 143 non-reactors on admission, who were followed six months to three years, 37 became reactors during the first year, 37 during the second year, and 10 during the third. Among 70 who were non-reactors on entrance, but were followed for three years, all but 10 became reactors.

Mariette says: "Still the possibility of infection exists in a sanatorium and this possibility constitutes a problem for the nurse who is caring for tuberculous individuals." In speaking of the nurse becoming infected he says: "In my opinion it is impossible for her to care for such patients very long without having an occasional bacillus gain entrance to her body."

Thus, although the tuberculosis situation with reference to infection had been markedly improved in the country as a whole, there had been created within the walls of our institutions a situation among our student nurses no

likely, and yielded to his sexual advances with enjoyment. This engagement failed to materialize; the patient believed the failure due to the interference of the doctor's brother, who she felt disapproved of her and of her father's modest occupation. That this experience was one of extreme difficulty for her was attested by the inconsistency in her attitude toward this man, for whom she had only the most hateful of epithets, yet whom obviously she still loved. Discouraged and embittered she developed an acute exacerbation of her symptoms, had her appendix removed because of chronic abdominal pain, and began to develop her vague, generalized tenseness. It will be noted that her constipation originally developed during the early years which she spent in conflict over caring for her mother and that the acute exacerbation of these symptoms took place immediately after the collapse of her marital dream.

Course: Atropine derivatives immediately relieved the patient's upper abdominal symptoms and reduced to a great extent her constipation and lower abdominal cramps. However, in view of her age, her rigidity of thought, and her drift toward hypochondriacal complaints it seemed wise to recommend more intensive psychotherapy, and this was done.

In the first of these cases the cause of emotional tension is readily understandable on the basis of the life situation. It may be argued that many young men could solve similar problems without the development of undue tension, which is true. A modifying factor in this case is the importance attached by the boy to his mother's opinion. Such a sense of dependence upon the opinion of one's mother is normal in childhood but is normally lost in adolescence. In this instance the patient lost his maternal dependence at age 21 with no great difficulty and with complete resolution of his problem. He certainly is correctly classified in the less neurotic group, although if the same situation were to evoke the same response at age 30, such classification would be doubtful. In this case the close association between emotional tension and the development of symptoms is obvious.

In the second case the cause for tension is clear enough, provided one can accept the premises which seem reasonable to the patient. These premises, however, are based on a rigid adherence to an unreasonable attitude. To a more flexible and resourceful individual many avenues of escape would be possible. Yet because this patient could not view her problems from a broader aspect she remained shackled. This peculiar rigidity of thought, with resentment against others, guilt, depression, and tension were frequently encountered in persons with not dissimilar histories. In this instance the association between social events, emotional tension, and symptoms is obvious enough. In some of the other more neurotic patients, however, such a direct relation could not be observed. The psychological processes were apparently so complicated that the chains of thought leading to the development of tension could not be demonstrated by the conversational method.

The evidence for psychological tension as a precipitating factor in mucous colitis cannot be reviewed here. It suffices to say that histories similar to those recounted can be obtained from the great majority of patients with mucous colitis. Such evidence is adequately presented elsewhere.<sup>7, 40</sup>

In 1930 Ross reported 60 students and graduates in nursing admitted to the Manitoba Sanatorium during the previous five years. In a more recent report he states that 75 others have been admitted. He says: "There is no doubt that the tuberculosis morbidity among nurses, especially nurses in training, is excessive and apparently increasing, as our second series is larger than the first, in spite of the fact that a new sanatorium in the Province now shares these cases with us." Thus, he reports 135 students or graduates in nursing who have been treated in his institution. He says: "Scores of students of nursing lose health and life through hospital-contracted tuberculous infections. Practically all students become tuberculin-positive during their course, showing that they have become infected even if disease should not follow. The hospital cannot avoid responsibility for the infection of nurses until the utmost of medical and nursing science has been used to prevent it."

In Saskatchewan, Ferguson made some observations on tuberculosis among nurses from 1930 to 1933 and found that 12 times as many students or recent graduates fall ill from this disease as other persons in the general population, and eight times as many as among normal school students, mostly girls, of almost the same age as the nurses.

Soper and Amberson state that "the Yale School of Nursing has not suffered particularly from tuberculosis in recent years." Of 191 students, who had roentgen-ray films on entrance and again on graduation over the last five years, two developed minimal parenchymal lesions and one other had pleurisy with effusion.

Badger and Spink observed student nurses in the Boston City Hospital with reference to tuberculosis over a five year period beginning January 1932. Of the 470 nurses observed 57.11 per cent were reactors on entrance to the school. Of the 126 nurses who completed their course 90 per cent were reactors on graduation. During this period of observation eight students developed lesions which were located by examination. One of the eight reacted to tuberculin on admission to the school; the remaining seven were non-reactors on admission but became reactors while in school.

Malmros and Hedvall examined 3,336 students and nurses and found 133 (4 per cent) with active tuberculosis. From this beginning they continued their studies, during which they observed 151 cases of fresh primary infection in adults, 104 of whom were free from symptoms and exhibited no evidence of disease except the tuberculin reaction. In the remaining 47, however, they were able to demonstrate lesions. These authors stated "that no less than thirty-five of these cases were students of medicine and nursing who through their work were exposed to massive infections of tubercle bacilli." From the examination and observation of 10,000 persons of various ages and various population groups in southern Sweden they stated that "the majority of cases of active tuberculosis in our material was among medical and nursing students. In this category of young persons one has to deal with an important occupational hazard."

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school except during the year 1937, when the seniors were encouraged but not compelled to take a six weeks' service in a sanatorium. The second student who elected this service returned with a strong tuberculin reaction. A few weeks later the roentgen-ray film revealed definite evidence of a lesion in the left upper lung field. The tuberculosis service was completely abandoned the following year. Therefore, for the most part, the girls in this school of nursing have had only the contact with tuberculous patients which might occur in any general hospital. The results of our observations on tuberculin reactions are shown in table 1, where it may be observed that among the entering classes the percentage of reactors ranged from 0 to 29.2, whereas on graduation this percentage ranged from 28.7 to 55.0.

TABLE I  
Comparison of Percentage of Tuberculin Reactors on Entrance with That on Graduation in School II

Year Graduated	Total Graduated	Reactors on Entrance		Reactors on Graduation	
		Number	Per Cent	Number	Per Cent
1932	14	3	21.4	4	28.7
1933	24	7	29.2	9	37.5
1934	24	3	12.5	12	50.0
1935	20	4	20.0	11	55.0
1936	0				
1937	13	0	0	7	53.9
1938	25	1	4.0	10	40.0

*Note:* Those who became reactors in training and discontinued their course are included as reactors on graduation.

In this school 120 student nurses were observed, 18 of whom reacted to the tuberculin test on entrance; 35 became reactors while in school, and 67 did not react to tuberculin on graduation. Of the 18 who entered as reactors one developed a demonstrable clinical lesion before graduation. One student on entrance in 1932 reacted strongly to tuberculin. Films of her chest at that time were clear. In 1933 there was evidence of disease in the apex of the right lung and at the level of the second interspace in the left lung where evidence of cavitation soon appeared. Tubercle bacilli were recovered from the sputum. Another student entered the school of nursing in the fall of 1935 as a tuberculin reactor. Roentgen-ray film in the fall of 1935 revealed evidence of calcification in the right hilum. In 1937 roentgen-ray film revealed evidence of disease in the right upper lobe.

Of the 35 who became reactors one had erythema nodosum with no other evidence of disease, and one developed a primary lesion demonstrable by roentgen-ray film in the left upper lobe.

Among the 120 graduates of this school 59 (49.2 per cent) replied to our questionnaire. Twenty-five (47.1 per cent) of them were previous tuberculin reactors, and 34 (50.7 per cent) were among the 67 who were non-reactors at the time of graduation. In this latter group 12 had the

## TUBERCULOSIS AMONG STUDENTS AND GRADUATES IN NURSING \*

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DURING the past decade there has been a widespread interest revived in the subject of tuberculosis among nurses, with particular emphasis on the transmission of the disease from patients to students and graduates of this profession. The danger of those who care for tuberculous patients contracting the disease has long been recognized, as evidenced by the following statement: "Isocrates (436-338 B.C.), pleading for the inheritance of a consumptive who had adopted him and whom he had nursed, exclaimed: 'I was in such a condition that all my friends, who came to visit me, expressed their fear that I perish with him, and pledged me to protect myself, telling me that most of those who had nursed this disease had become victims.'"

Aristotle said: "Why, when one comes near consumptives, or people with ophthalmia, or the itch, does one contract their disease, while one does not contract dropsy, apoplexy, fever, or many other ills? . . . In approaching the consumptive one breathes this pernicious air. One takes the disease because there is in this air something disease-producing."

In the literature of the centuries that followed there are numerous references to the contagiousness of consumption. A controversy was waged between those believing in the hereditary nature of tuberculosis and those believing in its contagiousness. Drastic laws were enacted and rigidly enforced to control contagion in such nations as Italy and Spain in the 18th century. It was not until the 19th century that overwhelming evidence was presented on the side of contagion through the experimental work of Klencke, Villemin, and Cohnheim, the epidemiological writings of Budd, and the bacteriological studies of Koch. During Koch's time tuberculosis was thought to be so prevalent that nearly every one had "a touch" of it. Pirquet found a high percentage of the young adults he examined to be tuberculin reactors. He was of the opinion that in the city in which he worked, as well as in the tuberculosis clinic, one might expect nearly all young adults to be infected, but he was inclined to believe that in other parts of the world, where there was not so much exposure of children to contagious cases of tuberculosis, the incidence of reactors would be lower.

Actual observations did not prove the point conclusively in this country until 1916 when Veeder and Johnston of St. Louis found that less than 50 per cent of school children reacted to tuberculin, and in 1924 when Slater

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TABLE III

Comparison of Percentage of Tuberculin Reactors on Entrance with That on Graduation, by Classes, School III

Year Graduated	Total Graduated	Reactors on Entrance		Reactors on Graduation	
		Number	Per Cent	Number	Per Cent
1932	29	3	10.3	15	51.7
1933	40	14	35	21	52.5
1934	Insufficient Data				
1935	44	12	27.3	18	40.9
1936	32	6	18.8	10	31.3
1937	28	5	17.8	9	32.1
1938	31	10	32.3	20	64.5

*Note:* All those who entered as non-reactors and became reactors in training are included as reactors on graduation.

areas of disease disseminated throughout the left lung and the upper lobe of the right lung. Tubercle bacilli were present in the sputum.

Unfortunately, in the earlier part of our work the roentgen-ray examination was not routine in this school; therefore, we saw only those students who actually developed symptoms.

Among the 204 graduates, 82 (40.2 per cent) replied to our questionnaire. Among the 93 who graduated as reactors, 34 (36.6 per cent) replied, and of the 111 who were graduated as non-reactors, 48 (43.3 per cent) replied. Twenty-three of those who were graduated as non-reactors reported having had the tuberculin test administered since graduation, five (21.5 per cent) of whom had become reactors. Therefore, we now know of 98 (48.0 per cent) of the graduates of this school who react to the tuberculin test. Of the 34 previous reactors who replied 23 have had recent roentgen-ray examinations of the chest, as also have 15 of the 48 previous non-reactors. Three of the graduates are known to have developed pulmonary lesions since graduation as follows:

*Case 1.* This nurse completed her training in 1931 as a non-reactor, after which she was engaged in private duty nursing. In 1935 she accepted a position in a hospital where she was in contact with tuberculous patients. Later the same year she was found to have definite evidence of disease in both upper lung fields. The tuberculin test was administered, and she was found to be a reactor. No symptoms have appeared and the shadows have decreased. She was treated by strict bedrest for approximately one year, but is now working on a full time basis.

*Case 2.* This nurse entered the school of nursing in the fall of 1929 and was graduated in the spring of 1932. Throughout the nursing course she was a non-reactor to tuberculin. Following graduation she was employed in a general hospital where she had contact with tuberculous patients. In 1937 a roentgen-ray film revealed evidence of a small area of disease in the apex of the right lung. She was admitted to a sanatorium in September 1937, and discharged in June 1938. At no time were any significant symptoms present. She is now working on a full time basis.

*Case 3.* This student entered the school of nursing as a non-reactor in the fall of 1931. Periodic tuberculin tests revealed no reaction throughout her course of nursing. Following graduation, in the spring of 1934, she was exposed to tubercu-

better than that of the time, place, and conditions of Pirquet's work. Along with this high infection attack rate among the students of nursing came the inevitable—mental anguish, illness, and death. With the recognition of the problem came attempts to solve it. Space does not permit more than a brief review of certain publications in this field, but the references contain many others.

The type of pulmonary lesions which students and recent graduates in nursing develop has been a subject of considerable controversy. In some series of cases reported there has been no previous tuberculin testing, and hence the determination of type is possible only through a long period of observation. In other series no attempt has been made to differentiate between the first infection and reinfection types, so that all lesions demonstrated by roentgen-ray film or otherwise are considered and treated as clinical disease. In other groups of cases a serious effort has been made to distinguish between the types of lesions which appear in the lungs, since treatment necessarily is dependent upon the type of lesion present.

Among 625 reactors on entrance to a school of nursing Heimbeck found that 27 developed conditions which he considered as evidence of clinical tuberculosis, whereas, among 280 who became reactors under his observation, 96 developed evidence of the disease in addition to the tuberculin reaction. However, in 39 of these students erythema nodosum and the tuberculin reaction were the only evidences of tuberculosis. Twenty-six others had only evidence of the primary complex located by roentgen-ray examination in the lung parenchyma, the hilum lymph nodes, or both. Sixteen others had pleurisy with effusion, two had fatal tuberculous meningitis, and 13 had clinical pulmonary tuberculosis.

Shipman and Davis of San Francisco, over a 10-year period of observation, found that between 6 and 7 per cent of the student nurses developed clinical tuberculosis and that an additional 4 per cent had developed the disease after graduation.

Among 110 student nurses observed by Geer of St. Paul, 5.5 per cent had developed lesions demonstrable by roentgen-ray or other phases of the examination by the time he made his report.

In 1934 Wicks of New Toronto, Ontario, wrote that "no nurse or attendant known to have entered his or her occupation with a positive tuberculin reaction has developed tuberculous disease during the past year, whereas six of those with a negative reaction on entrance have developed tuberculous lesions in the same period." Three of these persons had pleurisy with effusion; two had minimal parenchymal shadows with enlargement of the hilum shadows; and one mottling in the base of the right lung with evidence of small cavity formation and the presence of tubercle bacilli in the sputum.

Amberson and Riggins reported that among 492 student nurses eight developed new lesions while in school. Meulengracht found that 5 to 6.2 per cent of the nurses in a Danish training school developed tuberculosis.

plied. Of the 79 non-reactors on graduation who replied and have since been tested 27 (34.2 per cent) had become reactors since leaving school. Therefore, we now know of 396 who have reacted to the tuberculin test. Of the 174 reactors on graduation 136 replied that they had recent roentgen-ray films of the chest, and of the 113 non-reactors on graduation 40 had such examination.

Of the 165 who reacted on entrance four developed demonstrable lesions while in school and two after graduation:

*Case 1.* On entrance to the school of nursing in 1930 this student reacted to tuberculin. Films of her chest in 1931 revealed no evidence of disease. In 1932, however, there was evidence of disease in the left first interspace. This shadow persisted, and in 1934 it had extended. At this time there was also evidence of disease in the apex of the right lung.

*Case 2.* This student reacted to the tuberculin test on entrance to the school of nursing in 1932. Films of her chest through 1934 were negative. In 1935 there was definite evidence of disease in the upper lobe of the left lung. This shadow persisted through 1936, but could not be visualized in February 1938.

*Case 3.* This student reacted to tuberculin when she entered the school of nursing as a sophomore in 1932. Films of her chest in 1932 and 1933 were negative. In 1934 there was definite evidence of disease at the level of the first interspace on the left side. Her disease later increased and she had a pulmonary hemorrhage. The left phrenic nerve was interrupted and later artificial pneumothorax was instituted.

*Case 4.* This student entered the school of nursing in the fall of 1930 as a tuberculin reactor. Roentgen-ray films of the chest in 1931 and 1932 revealed evidence of fibrotic and nodular disease in the left lung, extending from the apex to the second rib. This was also present in September 1933.

*Case 5.* This student entered the school of nursing as a tuberculin reactor in the fall of 1930, but the roentgen-ray films of her chest revealed no evidence of disease. She discontinued school for reasons other than health. However, in the fall of 1935 she was found to have extensive disease involving the left lung from the apex to the level of the fifth rib anteriorly. There was definite evidence of cavitation, and tubercle bacilli were present in the sputum. Adhesions prevented successful artificial pneumothorax. Thoracoplasty was performed in 1936. She is now working on a full time basis.

*Case 6.* As a freshman in the school of nursing, in the fall of 1930, this student reacted to the tuberculin test. The roentgen-ray films of her chest revealed no evidence of disease through August 1933. In November 1933 a small lesion was discovered in the left infraclavicular region. In March 1936 there was evidence of disease in the right upper lung field. She was later hospitalized, and in March 1938 had far advanced disease with cavitation involving the right lung. Thoracoplasty is now being performed.

Of the 204 who became reactors as students 19 developed lesions demonstrable by roentgen-ray film or otherwise while in school, and five after graduation. The following developed only primary lesions which were demonstrated by roentgen-ray film:

*Case 7.* In the fall of 1929, as a freshman in a school of nursing, this student was a non-reactor to tuberculin. In the fall of 1931 she was a reactor. In December 1931 there was evidence of disease in both upper lung fields. The shadows gradually decreased until September 1936, when they had almost completely disappeared.

In addition to those quoted many others have reported on tuberculosis among students and graduates in nursing. From the available reports it is evident that there is a considerable difference in the degree of severity of the tuberculosis problem in various institutions.

In 1929 we began observations on students on entrance and throughout their courses of training. Our procedure began with the administration of the tuberculin test to all entering students. Those who did not react to the first dose (0.1 milligram) were given a second dose (1.0 milligram). Those who did not react to the second dose were retested in a similar manner at six-month intervals as long as they were non-reactors. All who reacted to the tuberculin test on admission or who subsequently became reactors were to have roentgen-ray films made of their chests at once and annually thereafter, except those in whom the findings warranted more frequent examinations. At the beginning of our studies the recommendation of roentgen-ray film examinations was frequently ignored since the relationship between a tuberculin reaction and clinical tuberculosis was not apparent. It was difficult to convince the schools that a girl in apparent excellent health with a tuberculin reaction might have clinical disease developing which would cast a definite shadow on the roentgen-ray film. Therefore, our early data are not as complete as we had desired. However, during the latter part of our period of observation all the schools were coöperative to the fullest extent.

In 1938 we sent a questionnaire containing the following questions to those who graduated as non-reactors:

1. Have you had the tuberculin test repeated since you left the school of nursing? If so, please give approximate dates and the results; that is, was the test negative or positive?
2. If your test has become positive, have you had any roentgen-ray films made of your chest? If so, on what approximate dates and were any abnormal shadows found in your lungs?
3. Have you had any illness since leaving school, such as pleurisy or disease of the lungs?

The following questions were sent to those who were reactors on graduation.

1. Have you had any roentgen-ray films made of your chest since leaving the school of nursing? If so, on what approximate dates and were any abnormal shadows found?
2. Have you had any illness since leaving school, such as pleurisy or disease of the lungs?

## SCHOOL OF NURSING II

In School II classes were admitted every year except 1933; therefore, there were no graduates in 1936. There was no tuberculosis service in this

tuberculin test was not repeated at this time. In March the shadow had decreased somewhat in size, and she reacted to tuberculin. This student cancelled her registration and we have been unable to obtain further information concerning her.

None of these students was ill and we consider them as not differing from all the others who became reactors, except that one of the primary foci in each case was so situated that it could be seen in a roentgen-ray film.

The following had pleurisy with effusion while in school:

*Case 17.* As a freshman in the school of nursing, in July 1929, this student was a non-reactor to tuberculin. In May of 1931 she was found to be a reactor. In the spring of 1931 she had pleurisy with effusion on the left side while taking a tuberculosis service. She was admitted to a sanatorium on June 1, 1931, where she remained until August 31, 1931. A roentgen-ray film in November 1932 revealed evidence of adhesions in the left costophrenic angle, but no evidence of disease in either lung. In February 1933 a film revealed no change. On December 23, 1938, she wrote that she was enjoying excellent health and was employed as an instructor in a school of nursing.

*Case 18.* As a freshman in the school of nursing, in the fall of 1931, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the spring of 1935, when she was a reactor. All roentgen-ray films were clear until August 1935, when she had pleurisy with effusion on the right side. She cancelled out of school on March 8, 1936, but returned in the spring of 1937. In May 1937 the roentgen-ray film revealed evidence of disease in the left lung extending from the apex to the second rib, and in the second interspace on the right side. She again left school and was admitted to a sanatorium on June 28, 1937, where she remained until November 24, 1937, with a diagnosis of minimal pulmonary tuberculosis. At no time were tubercle bacilli found in her sputum. She has not returned to school.

*Case 19.* As a freshman in the school of nursing, in the fall of 1929, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until October 1930, when she was found to be a reactor. A roentgen-ray film of the chest at that time was clear. In November 1930 she had pleurisy with effusion. After several months the fluid absorbed and roentgen-ray films of the chest were clear through the summer of 1938.

*Case 20.* As a freshman in the school of nursing, in the fall of 1930, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until May 15, 1933, when she was found to be a reactor. Previous roentgen-ray films of the chest were clear, but on May 19, 1933, pleurisy with effusion was present. The fluid had absorbed by the fall of 1933. In July 1933 a small area of disease was detected in the right lung at the level of the second and third interspaces. In November 1933 an area of disease was demonstrated in the first interspace on the left side. In January 1935 the shadow in the right lung was sharply outlined and that in the left lung had almost entirely disappeared. She was in a sanatorium from July 1936 to June 1937, when her disease was classified as arrested.

We look upon pleurisy with effusion in this group as a result of the sensitiveness of the tissues to tuberculo-protein and to endogenous reinfection from the primary foci.

The following developed demonstrable lesions which probably represent the reinfection type:

*Case 21.* On entrance to the school of nursing, in the fall of 1930, this student was a non-reactor to tuberculin. In the spring of 1932 she reacted to tuberculin, but

tuberculin test administered since graduation, two of whom had become reactors (16.6 per cent). Therefore, we now know of 55 (45.8 per cent) of the graduates of this school who have reacted to the tuberculin test. Of the 25 previous tuberculin reactors who replied to our questionnaire 12 reported having had recent roentgen-ray examinations of the chest, and of the 34 non-reactors who replied five reported such examinations. One nurse who was a non-reactor on graduation in 1933 reported having developed a condition of the ankle, following an injury, which was diagnosed tuberculous in March, 1938, but the roentgen-ray films of her chest were clear. She was found to be a tuberculin reactor in February 1938, after the injury to her ankle.

In table 2 the results of tuberculin tests and the lesions located on roentgen-ray film or otherwise are summarized.

TABLE II  
School of Nursing II  
(No Tuberculosis Service)

18 with primary complexes on entrance	
a. Lesions while in school	2 (11.1 per cent)
b. Lesions since graduation	0
35 developed primary complexes while in school	
a. Lesions detected while in school	1 (2.8 per cent)
b. Lesions after graduation	0
2 developed primary complexes after graduation	
Lesions detected	1

### SCHOOL OF NURSING III

In School III classes were admitted every year, but the data for the class graduating in 1934 are incomplete; therefore, this class is omitted from our report. There was no tuberculosis service in this school, but in 1937 an increased number of advanced cases of tuberculosis was admitted. Therefore, until 1937 the girls in this school of nursing had such contact with tuberculous patients as might be found in any general hospital that admits the occasional patient for diagnosis and treatment and the occasional unsuspected case that is admitted for some other condition.

On entrance the percentage of reactors among the classes ranged from 10.3 to 35.0, whereas on graduation it ranged from 31.3 to 64.5 (Table 3).

In this school 204 student nurses were observed, 50 of whom reacted to the tuberculin test on entrance, 43 of whom became reactors while in school, and 111 of whom still did not react to the test on graduation. Of the 50 who entered as reactors three had demonstrable reinfection type of lesions at the time; none developed demonstrable lesions while in school. Of the 43 who became reactors while in school one developed a primary lesion, demonstrable by roentgen-ray film, which later resolved. Another student who entered as a non-reactor in 1933 reacted strongly to the test in March 1934. At that time a film of her chest revealed no evidence of disease. However, in December 1935 she was ill and there was definite evidence of

school of nursing as a junior in the fall of 1931. She was found to be a definite reactor in April 1933. Roentgen-ray films of her chest in January and April 1933 revealed no evidence of disease. In August 1935 roentgen-ray film examination revealed evidence of disease involving the left lung at the level of the first and second interspaces. The shadows have remained unchanged.

*Case 28.* This student entered the school of nursing in the fall of 1934 as a non-reactor to tuberculin. She was still a non-reactor in 1935. In May 1937 she was found to be a reactor. Roentgen-ray films in June 1936 and September 1936 were negative. In May 1937 there was possible calcification in the left hilum. There was evidence of disease in the left lung at the level of the second interspace. This shadow was still present in May 1938, but could not be visualized in November 1938.

*Case 29.* This student entered a school of nursing as a junior in the fall of 1930, at which time she was a non-reactor to tuberculin. In the fall of 1931 she still did not react to the tuberculin test. However, in June 1932 she became a reactor. Roentgen-ray films of her chest on several occasions in 1932 and 1933 revealed no evidence of disease. In January 1934 she had pleurisy with effusion. The effusion absorbed, and in 1938 the lungs were clear on roentgen-ray film examination.

*Case 30.* On entrance to the school of nursing, in the fall of 1929, this student was a non-reactor to tuberculin. When she was graduated in 1932 she was a reactor. In the summer of 1933 she was employed in a sanatorium. At that time the roentgen-ray film examination of her chest revealed no evidence of disease. Periodic films were clear through January 1936. On June 11, 1936, a shadow was present in the right lung at the level of the first, second and third interspaces. In August 1936 the lesion had increased in size. She was then hospitalized, and in February 1937 artificial pneumothorax was instituted. Tubercle bacilli were never recovered from the sputum, and there were no symptoms except a slight cough at the time she was admitted to the sanatorium. She was discharged from the sanatorium on June 15, 1937, but continued on artificial pneumothorax through December 1938.

The following seven former students graduated as non-reactors but later developed lesions:

*Case 31.* This student entered the school of nursing in 1929 as a non-reactor to tuberculin and did not react while in school or on graduation in 1932. Following graduation she was employed in a sanatorium, and in January 1933 was found to be a reactor. In 1933 she was found to have a shadow on the roentgen-ray film at the level of the right second interspace. In June 1933 the shadow had decreased in size. Subsequent periodic films revealed a gradual disappearance of the shadow. On December 1, 1938, there was evidence of a probable small calcium deposit at the site of the previous shadow.

*Case 32.* As a freshman in the school of nursing, in the spring of 1931, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction throughout her course. Films of her chest were clear in October 1934. Immediately following graduation in the spring of 1935 she was employed in a sanatorium, and in October 1935 she reacted to tuberculin. At that time films of her chest were clear. In December 1935 she had pleurisy with effusion. She was admitted to the sanatorium where she worked on December 28, 1935. Films of the chest in January 1936, after the fluid had absorbed, revealed no evidence of disease in either lung. However, in March 1936 there was evidence of a large parenchymal lesion with cavitation in the right lung. Artificial pneumothorax was instituted and she is still on that treatment in the sanatorium.

*Case 33.* This student did not react to tuberculin when she entered the school of nursing as a junior in October 1931. She was graduated in June 1933. In August and September of 1933 she worked in a sanatorium, and in the fall of that year was

losis from August 1937 to March 1938, and in December 1937 she was found to be a tuberculin reactor. In March 1938 roentgen-ray films revealed a definite shadow in the right second interspace. She had no symptoms at any time. The last film, made in November 1938, revealed a marked decrease in the shadow. She did not discontinue her work on account of this lesion.

In table 4 the results of tuberculin tests and the lesions located by roentgen-ray film or otherwise are summarized.

TABLE IV  
School of Nursing III  
(No Tuberculosis Service)

50 with primary complexes on entrance	
a. Lesions while in school	0
b. Lesions since graduation	0
43 developed primary complexes while in school	
a. Lesions detected while in school	2 (4.7 per cent)
b. Lesions since graduation	0
5 developed primary complexes after graduation	
Lesions detected	3

#### SCHOOL OF NURSING IV

In School IV all students were required to spend six weeks in residence in a sanatorium before graduation. In this school it was found that 41 nurses had completed the course without having the tuberculin test administered within nine months of graduation; therefore, they are not included in this report. Table 5 shows that the percentage of reactors among the classes

TABLE V  
Comparison of Percentage of Tuberculin Reactors on Entrance with That on Graduation,  
School IV

Year Graduated	Total Graduated	Reactors on Entrance		Reactors on Graduation	
		Number	Per Cent	Number	Per Cent
1932	94	24	25.5	69	73.4
1933	85	40	47.1	64	75.3
1934	98	33	33.7	65	66.3
1935	87	23	26.4	54	62.1
1936	62	11	17.7	38	61.3
1937	62	15	24.2	40	64.5
1938	62	19	30.6	39	62.9

on entrance ranged from 17.7 to 47.1, but that on graduation this percentage ranged from 61.3 to 75.3.

In this school 550 student nurses were observed, of whom 165 reacted to tuberculin on entrance; 204 became reactors while in school; and 181 did not react to tuberculin on graduation.

Of the 550 graduates, 287 (52.2 per cent) replied to our questionnaire. From the 369 who were graduated as reactors 174 (47.1 per cent) replied. Of the 181 who were graduated as non-reactors 113 (62.4 per cent) re-



## SCHOOL OF NURSING I

In School I all students were compelled to spend three months during the senior year on a 30-bed tuberculosis service in the hospital. This service was abandoned in 1935, so the class graduating in 1938 was the first one to pass through the school of nursing after the tuberculosis service was removed from the hospital. The results of our observations on tuberculin reactions are shown in table 7, where it will be observed that among the entering classes the percentage of reactors ranged from 2.4 to 44.4, whereas on graduation this percentage ranged from 40.5 to 100.

TABLE VII

Comparison of Percentage of Tuberculin Reactors on Entrance with That on Graduation, School I

Year Graduated	Total Graduated	Reactors on Entrance		Reactors on Graduation	
		Number	Per Cent	Number	Per Cent
1932	36	16	44.4	36	100
1933	41	5	12.2	37	90.2
1934	26	10	38.5	25	96.1
1935	30	6	20.0	28	93.3
1936	25	4	16.0	20	80.0
1937	26	6	23.1	22	84.6
1938	42	1	2.4	17	40.5

*Note:* Those who became reactors in training and discontinued their course are included as reactors on graduation.

In this school 226 nurses were observed, 48 of whom reacted to the tuberculin test on entrance, 137 of whom became reactors while in school, and 41 of whom did not react to tuberculin on graduation.

Of the 226 students in this school 140 (61.9 per cent) replied to the questionnaire. Of the 185 reactors on graduation 121 (65.4 per cent) replied, and of the 41 non-reactors 19 (46.3 per cent) replied. Nine of the previous non-reactors reported having had the tuberculin test administered since graduation, but none had reacted to the test. There were 58 (47.9 per cent) of the 121 former reactors who reported having had recent roentgen-ray film examinations of the chest, and four of the 19 previous non-reactors who reported having had such examination.

Of the 48 entering as reactors two had primary lesions demonstrable by roentgen-ray film on entrance which later resolved. The following later developed clinical disease:

*Case 1.* In the spring of 1929, as a freshman in the school of nursing, this student was a tuberculin reactor. Roentgen-ray films of her chest in 1929 and 1930 were clear. On April 30, 1931, cloudiness was reported over both apices. In November 1934 she had pleurisy with effusion.

*Case 2.* On entrance to the school of nursing in the fall of 1932 this student was a tuberculin reactor. Periodic roentgen-ray films made throughout her course of training revealed no evidence of disease. In the spring of 1937, while employed

*Case 8.* In the fall of 1932, as a freshman in the school of nursing, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the fall of 1934, when she was a definite reactor. All roentgen-ray films were clear until September 1935, when there was definite evidence of disease in the left second and third interspaces. The shadow had decreased somewhat in February 1936.

*Case 9.* In the fall of 1931, as a freshman in the school of nursing, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the fall of 1934. All roentgen-ray films were clear until May 1935, when an area of disease appeared in the upper lobe of the left lung. The shadow gradually decreased until the summer of 1937 when it had completely disappeared.

*Case 10.* As a freshman in the school of nursing, in the fall of 1933, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until April 22, 1934. On May 8, 1934, there was evidence of a small area of disease at the level of the right second interspace. The shadow increased somewhat during the next two or three months, when she was advised to take treatment. She never returned to school. Subsequent films, including those in the spring of 1936 and the summer of 1937, revealed no change in the shadow.

*Case 11.* In the fall of 1929, as a freshman in a school of nursing, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until January 1934. At this time there was definite evidence of disease at the level of the first interspace on the left side. The subsequent films showed a gradual decrease in the lesion until 1936. Since that time, including the summer of 1938, the shadow has remained unchanged.

*Case 12.* In the spring of 1934, as a student of nursing, this girl was a non-reactor to tuberculin. Periodic tests revealed no reaction until the winter of 1937. At that time there was definite evidence of disease in the right second and third interspaces.

*Case 13.* As a freshman in the school of nursing, in the fall of 1933, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the spring of 1937. On December 28, 1936, there was evidence of disease in the right second interspace. The shadow appeared essentially unchanged through April 1937.

*Case 14.* As a freshman in the school of nursing, in the fall of 1932, this student was a non-reactor to tuberculin. In the winter of 1934 she was assigned to a tuberculous patient who died of the disease. She had some minor illnesses in the spring of 1934 and cancelled out of school. In March 1934 she reacted to tuberculin. In the summer of 1934 she was found to have an area of disease in the right sub-clavicular region and was advised by her physician to take a six months' period of bed rest. She never returned to school, but in the summer of 1936 her physician stated that she was cured. In February 1937 the roentgen-ray film revealed small densities suggestive of calcium deposits at the site of the disease. In December 1938 she was apparently well.

*Case 15.* In the fall of 1933, as a freshman in the school of nursing, this student was a non-reactor to tuberculin. On May 21, 1934, she was still a non-reactor. On April 22, 1935, she reacted to tuberculin. A roentgen-ray film of the chest in October 1933 was clear. In May 1935 a roentgen-ray film revealed definite evidence of disease in the right first interspace. Periodic roentgen-ray films through 1935 revealed no change in the shadow. In April 1936 the shadow had decreased in size. Throughout the remainder of 1936 there was no change. By September 1937 the shadow had completely disappeared. In February 1938 the film was apparently clear.

*Case 16.* In the fall of 1933 this student entered the school of nursing as a non-reactor. At that time films of the chest revealed no evidence of disease. In February 1934 a shadow appeared in the first and second interspaces on the left side, but the

change was observed in July 1937. She was graduated in 1937, and in December 1938 she was working as an operating room nurse, apparently in excellent health.

*Case 9.* In the fall of 1932 this student entered the school of nursing as a non-reactor. She did not react to tuberculin until March 1934. In April of the same year a small area of disease appeared in the base of the right lung. In May 1934 this had definitely increased in size. Because of the occurrence of a small pulmonary hemorrhage, and the finding of tubercle bacilli in the sputum, artificial pneumothorax was instituted. She was graduated in 1936 and has continued on artificial pneumothorax treatment.

*Case 10.* As a freshman in the school of nursing, in the spring of 1933, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until October 1935, when she was found to be a reactor. All films of her chest were clear through September 1935. In April 1936 a lesion was present in the left lung extending from the apex to the first interspace. No treatment was administered, and in December 1938 she was working full time as a school nurse.

*Case 11.* This student entered the school of nursing in the fall of 1934 as a non-reactor to tuberculin. There was no test in 1936. She was a reactor in March 1937. Pleural effusion was found May 1, 1936, on the right side, and was still present June 5, 1936. In June 1937, the effusion was gone and her chest was clear.

*Case 12.* As a freshman in the school of nursing, in the fall of 1934, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the fall of 1936, when she was found to be a reactor. In 1934 the roentgen-ray film of her chest was clear. In October 1936 there was evidence of disease at the level of the second rib on the right side. Films made on December 13, 1936, February 18, 1937, and April 6, 1937, revealed no change in the shadow. On August 27, 1937, the film was clear.

*Case 13.* As a freshman in the school of nursing, in the fall of 1934, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until the spring of 1936. Roentgen-ray films of the chest were clear until the spring of 1936, when there was evidence of disease in the right third interspace. In the summer of 1936 there was evidence of pleurisy at the right base, but no evidence of fluid was observed. In the fall of 1936 there was evidence of considerable thickening of the pleura over the right base and marked elevation of the right side of the diaphragm. In December 1938 she was still in school, and the film revealed no evidence of disease in either lung.

Of the 137 who became reactors while in school we know of the following who developed demonstrable lesions after graduation:

*Case 14.* This student entered the school of nursing in the fall of 1930 as a non-reactor to tuberculin. In March 1932 she reacted to tuberculin. Films in 1930, 1931, and 1932 revealed no evidence of disease. In December 1935 she had evidence of tuberculous lesions in the left upper lobe. There have been no significant symptoms, and she was working as a nurse in January 1939.

*Case 15.* This student entered the school of nursing in the fall of 1930 as a non-reactor to tuberculin. She became a reactor in 1932. Roentgen-ray films in 1930, 1932, and 1933 revealed no evidence of disease. In January 1938 she developed pain in the chest. Examination revealed evidence of disease involving the right lung from the apex to the third rib. There was also evidence of disease in the left lung at the level of the third interspace near the periphery. Tubercle bacilli were present in the sputum. She was admitted to a sanatorium, where artificial pneumothorax was instituted on the right side. She is still a patient in the sanatorium and has continued on artificial pneumothorax.

the roentgen-ray films of her chest revealed no evidence of disease. In December 1932 a small area of disease was found in the left lung at the level of the second interspace. In May 1933 the area of disease was considerably larger and there was possible beginning cavity formation. She was then admitted to a sanatorium and artificial pneumothorax was instituted. She was discharged from the sanatorium in August 1935, but continued on artificial pneumothorax treatment.

*Case 22.* This student was a non-reactor to tuberculin on entrance to a school of nursing in the fall of 1929. Roentgen-ray films of the chest at that time were clear. In July and August 1931 there was evidence of thickened pleura on the left side and a small area of disease at the level of the second interspace in the left lung. A tuberculin test was said to have been administered at this time but there was no reaction. In January 1934, although strict bedrest had previously been employed, a small area of disease was found at the level of the third interspace on the right side. At this time she reacted strongly to tuberculin. She has had prolonged strict bedrest, and although her general health is good she still has definite shadows in both lungs.

*Case 23.* This student was a non-reactor to tuberculin when she entered the school of nursing in the fall of 1929. Roentgen-ray films of her chest were clear. She was still a non-reactor in September 1930. On June 9, 1932, she was admitted to a sanatorium with diagnosis of tuberculosis of the spine. She was discharged May 20, 1934. Spinal condition was good in June 1937. Roentgen-ray films of her chest revealed no evidence of clinical disease at any time including February 19, 1938. She did not return to complete the course in nursing.

*Case 24.* This student did not react to tuberculin on entrance to a school of nursing in the fall of 1931. In the spring of 1933 she was a definite reactor. All films of the chest, including those of the spring of 1935, were clear. In the summer of 1935 there was definite evidence of disease in the apex and first interspace on the left side. She was hospitalized for four and one-half months but no symptoms appeared. The films revealed no change in shadow through February 1936. In August 1937 she had extension of lesion with cavity formation. She has since been treated by artificial pneumothorax.

*Case 25.* On entrance to a school of nursing, in the fall of 1932, this student did not react to tuberculin. Roentgen-ray films of the chest were clear. In the spring of 1933 she was found to be a reactor. Roentgen-ray films of the chest through July 1934 revealed no evidence of disease. In November 1934 there was a definite area of disease present in the left lung at the level of the first interspace. In April 1935 the area in the left lung had increased in size, and there was a definite area of disease in the right lung at the level of the third and fourth interspaces. In April 1935 there was evidence of definite increase of the shadow in the right lung. She was hospitalized and artificial pneumothorax was instituted in August 1935. Empyema was present in December 1935. In August 1937 the empyema had disappeared and she was still being treated by artificial pneumothorax in a sanatorium.

The following students who became infected while in school developed lesions which were demonstrated after graduation:

*Case 26.* When this student entered the school of nursing in the fall of 1930 she did not react to tuberculin. She remained a non-reactor through August 1933. In the spring of 1934 she was found to be a reactor. Although previous roentgen-ray films of her chest had been negative she now showed evidence of pleurisy at the left base. This evidence had disappeared by January 1935. In October 1936 she was found to have extensive pulmonary tuberculosis involving the lower half of the right lung. Tubercle bacilli were present in her sputum. Artificial pneumothorax was instituted in October 1936, and her lung is still collapsed.

*Case 27.* This student was a non-reactor to tuberculin when she entered the

no more persons with tuberculosis than other members of the general population, whereas students in the schools of nursing may come in contact with tuberculous patients as a part of their work. In the College of Education we found 24.8 per cent of the students were reactors on entrance and 28.5 per cent on graduation (table 10). One sees that the percentage of tuber-

TABLE X

School	Number of Students	Per Cent Reactors Entrance	Per Cent Reactors Graduation	Per Cent of Non-Reactors* Who Became Reactors
Education	224	24.8	28.5	5.3
Nursing II	120	15.0	41.2	34.3
Nursing III	204	24.5	45.6	27.9
Nursing IV	550	30.0	67.1	53.0
Nursing I	226	21.2	81.8	77.0

\* Increase in Tuberculin Reactors Among Students in a College of Education and in Four Schools of Nursing from Entrance to Graduation.

culin reactors on graduation from schools of nursing in general hospitals which do not have tuberculosis services is definitely higher than in the Col-

PER CENT OF TUBERCULIN REACTORS AMONG  
STUDENT NURSES AND  
COLLEGE OF EDUCATION STUDENTS

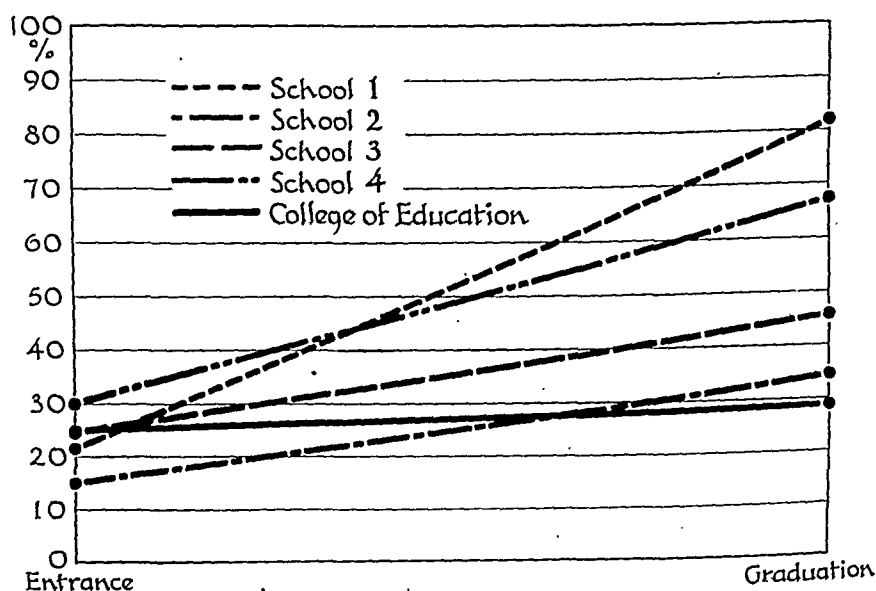


FIG. 1.

lege of Education. On the other hand, students in schools which have tuberculosis services have a much higher percentage of reactors on graduation than those from schools which have no tuberculosis service (figure 1). From the standpoint of demonstrable lesions there is also a sharp contrast

found to be a reactor, but the roentgen-ray films of her chest were clear. In January 1936 there was definite evidence of disease in each lung at the level of the first interspace. No symptoms developed. Strict bedrest was instituted. She is still in a sanatorium.

*Case 34.* This student entered the school of nursing in September of 1931 as a non-reactor. She still did not react to the tuberculin test when she was graduated in 1934. She was later employed in a hospital which had a tuberculosis service. In April 1937 she was found to have evidence of scattered areas of disease in the upper one-third of the left lung. She was hospitalized from May 7, 1937 until June 24, 1937. On May 13, 1937, the left phrenic nerve was interrupted. No symptoms were present at any time. On discharge from the hospital she returned to her home to continue treatment.

*Case 35.* On entrance to the school of nursing in 1932 this student was a non-reactor to tuberculin. Periodic tuberculin tests throughout her course revealed no reaction. Immediately following graduation she was employed in a sanatorium for four months, after which she worked on a chest surgery service for some time. While working in the sanatorium, in 1935, she was found to react to tuberculin, but the roentgen-ray film of her chest was clear. In March 1937 the roentgen-ray film revealed definite evidence of disease in both lungs, with cavitation in the right. Tubercle bacilli were found in the sputum in April 1938. Films in August 1937 and April 1938 showed no change. In October 1938 there was evidence of definite decrease in the shadows, and the cavity appeared to be reduced in size. She has been treated only by strict bedrest.

*Case 36.* This student entered the school of nursing as a non-reactor in the fall of 1933, and was graduated in 1936 as a non-reactor. Following graduation she worked on a tuberculosis service, and in the fall of 1936 was found to react to tuberculin. Roentgen-ray films of the chest while a student, including March 1937, revealed no evidence of disease. In March 1938 she had pleurisy with effusion on the left side. There was still some fluid present in October 1938. Tubercle bacilli were recovered from the fluid.

*Case 37.* In the fall of 1933 this student entered the junior class of the school of nursing as a non-reactor, and she did not react to tuberculin on graduation in 1935. Following graduation she worked for approximately two years in a sanatorium. In January 1936 she was found to be a reactor. When she discontinued sanatorium work roentgen-ray films of her chest were reported as revealing no evidence of disease. In November 1938 she was found to have pulmonary tuberculosis, with cavity formation in the right upper lobe. She was then admitted to the sanatorium where she had previously worked and artificial pneumothorax was instituted.

In table 6 the results of tuberculin tests and the lesions located by roentgen-ray film or otherwise are summarized. See table 9 for types of lesions.

TABLE VI  
School of Nursing IV  
(Six Weeks' Tuberculosis Service)

165	with primary complexes on entrance	
	a. Lesions while in school	4
	b. Lesions since graduation	2
		} (3.6 per cent)
204	developed primary complexes while in school	
	a. Lesions detected while in school	19
	b. Lesions since graduation	5
		} (11.8 per cent)
27	developed primary complexes after graduation	
	Lesions detected	7

## SUMMARY

1. A brief review of the literature reveals the fact that tuberculosis among student and graduate nurses is a serious problem in various parts of the world.

2. Our report consists of observations made in four schools of nursing since 1929. Students in a College of Education have been used as a control group.

3. In School II, where there is no tuberculosis service, 120 students were under observation. Eighteen were tuberculin reactors on entrance; 35 became reactors while in school, and 67 were graduated as non-reactors. Two of the students who entered as reactors developed pulmonary tuberculosis while in school; one of the 35 who became reactors had a primary focus in the lung parenchyma demonstrated by roentgen-ray film examination.

4. There was no tuberculosis service in School III. Here 204 students were observed, of whom 50 were reactors to tuberculin on entrance, 43 became reactors while in school, and 111 were graduated as non-reactors. None of those who reacted to the tuberculin test on entrance developed demonstrable lesions while in school. Of those who became reactors one developed a primary focus in the lung demonstrable by roentgen-ray film examination, and one developed bilateral clinical disease more than 18 months after she was known to be a reactor.

5. In School IV a six weeks' tuberculosis service was required of each student. Five hundred and fifty students were observed, of whom 165 reacted to tuberculin on entrance. Two hundred and four became reactors while in school, and 181 were graduated as non-reactors. Of the 165 who entered as reactors four developed demonstrable lesions while in school and two after the time of graduation. Of the 204 who became reactors as students 19 developed lesions demonstrable by roentgen-ray film or otherwise while in school, and five after the time of graduation (table 9).

6. In School I there was a 12 weeks' tuberculosis service during the first part of our period of observation. Here 226 students were observed, 48 of whom reacted to tuberculin on entrance, 137 of whom became reactors while in school, and 41 of whom were graduated as non-reactors. Among those who entered as reactors two developed lesions demonstrated by roentgen-ray film or otherwise while in school or after graduation. Of those who became reactors 14 developed demonstrable lesions while in school or after graduation (table 9).

7. In Schools II, III, and IV a questionnaire revealed the fact that some of the non-reactors on graduation had since become infected and a few had developed lesions demonstrated by roentgen-ray film or other methods.

8. We consider that every reactor to tuberculin has one or more primary tuberculosis complexes in the body. In this group the number who have developed demonstrable lesions located by roentgen-ray, etc., or who have

as a nurse in a general hospital, she was found to have tuberculosis involving the left lung from the apex to the third rib and the extreme apex of the right lung. No symptoms were present. Artificial pneumothorax was instituted in the spring of 1937. She is still receiving this treatment and has continued to work.

Of the 137 who became reactors as students we know of the following 11 who developed demonstrable lesions while in school, and of three who developed lesions after graduation:

*Case 3.* As a freshman in the school of nursing, in the fall of 1929, this student was a non-reactor to tuberculin. She was still a non-reactor in March 1930, but in September 1930 she was a reactor. No roentgen-ray film was made until July 1931, when there was evidence of disease in the left upper lung field, extending from the apex to the level of the second rib. In September 1931 the shadow had decreased somewhat, but she discontinued training in September 1931 because of the shadow. There were never any clinical manifestations.

*Case 4.* This student entered the school of nursing in the fall of 1929 as a non-reactor. She reacted to tuberculin in the fall of 1930. Roentgen-ray films revealed no evidence of disease. In July 1931 there was evidence of disease involving both lungs at the level of the first and second interspaces. Following this she was on bed-rest for a year, during which time the shadows on the roentgen-ray film decreased in size. She returned to school in 1932. In the spring of 1933 there was definite evidence of disease in the left lung, with evidence of small cavity formation. She was placed on treatment, but in November 1935 she developed tuberculous pneumonia in the base of the left lung and died in November 1936.

*Case 5.* When this student entered the school of nursing in the spring of 1930 she was a non-reactor to tuberculin. In May 1931 she reacted to tuberculin. Films of her chest were clear in March 1930, but in October 1931 there was evidence of disease in the right first interspace. She was hospitalized from October 8, 1931 until July 5, 1932. She discontinued training and did not return. Pneumothorax was instituted while in the hospital. She discontinued artificial pneumothorax in 1936 and apparently was in good health in December 1938.

*Case 6.* As a freshman in the school of nursing, in the fall of 1931, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until February 1933, when she was found to be a reactor. Roentgen-ray films of the chest were clear until February 1933, when there was evidence of disease in the left upper lobe. In March there was evidence of effusion in the left pleural cavity. In April the fluid had practically disappeared, but the left costophrenic angle was obliterated. In June 1935 there was evidence of Ghon tubercle formation in the left lung at the site of the previous area of disease. At this time there was also seen a small but definite area of disease in the extreme apex of the left lung. She was apparently in good health in December 1938.

*Case 7.* This student entered the school of nursing as a non-reactor in the fall of 1932. In the spring of 1933 she reacted strongly to tuberculin. In the summer of the same year an area of disease was located in the right lung at the level of the first and second interspaces. By February 1934 this shadow had completely disappeared. In March 1934 she was found to have tuberculous pneumonia involving the right upper lobe. She later developed empyema, and died in May 1935.

*Case 8.* As a freshman in the school of nursing, in the fall of 1932, this student was a non-reactor to tuberculin. Periodic tuberculin tests revealed no reaction until March 1934, when she was found to be a reactor. Roentgen-ray films of the chest were clear until August 1934, when there was evidence of fluid on the left side. She cancelled her registration and did not return until January 1936. At this time the only abnormal finding was partial obliteration of the left costophrenic angle. No



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*Case 16.* In the fall of 1931 this student entered the school of nursing as a non-reactor. In the spring of 1933 she reacted to tuberculin. Roentgen-ray films in 1932, 1933, and April 1934 were clear. However, in February 1935 there was definite evidence of disease involving the left lung from the apex to the second rib. Artificial pneumothorax was instituted and this treatment has been continued to the present time.

In table 8 the results of tuberculin tests and the lesions located by roentgen-ray film or otherwise are summarized.

TABLE VIII

## School of Nursing I

(Twelve Weeks' Tuberculosis Service)

48 with primary complexes on entrance	
<i>a.</i> Lesions while in school	1
<i>b.</i> Lesions since graduation	1
	} (4.2 per cent)
137 developed primary complexes while in school	
<i>a.</i> Lesions detected while in school	11
<i>b.</i> Lesions since graduation	3
	} (10.2 per cent)
0 developed primary complexes after graduation	

In table 9 we have indicated the percentages of those who developed primary and clinical lesions in Schools IV and I. See table 9 for types of lesions.

TABLE IX

## School of Nursing IV

(Six Weeks' Tuberculosis Service)

204 developed primary complexes while in school	
24 (11.8 per cent) location of lesions detected	
10 (4.9 per cent) primary foci only	
2 (1.0 per cent) pleural effusion only	
1 (0.5 per cent) effusion and primary focus	
11 (5.4 per cent) probable to definite clinical lesions	

## School of Nursing I

(Twelve Weeks' Tuberculosis Service)

137 developed primary complexes while in school	
14 (10.2 per cent) location of lesion detected	
4 (2.9 per cent) primary foci only	
2 (1.5 per cent) pleural effusion only	
1 (0.73 per cent) effusion and primary focus	
7 (5.1 per cent) probable to definite clinical lesions	

## School of Education

686 reactors	
3 (0.44 per cent) location of lesions detected	
1 (0.15 per cent) primary focus only	
2 (0.29 per cent) clinical lesions	

## COLLEGE OF EDUCATION

When this study began we saw the need for a control group of students for observation. We selected the College of Education because its students are of approximately the same age as those in the schools of nursing and have been reared in the same types of communities. The only essential difference is that students in the College of Education come in contact with

# ARTERIAL OXYGEN SATURATION IN CIRRHOSIS OF THE LIVER\*

By ROBERT C. DARLING, M.D., *New York, N. Y.*

THE finding of a severe degree of oxygen unsaturation in the arterial blood of patients with cirrhosis of the liver has been reported by Snell.<sup>1</sup> Later, Keyes and Snell<sup>2</sup> studied a further series with oxygen dissociation curves, and found a small but significant shift in the curve from the accepted normal value. In this second series the oxygen unsaturation of the arterial blood was less marked than in the first series. From this work it was concluded that the hemoglobin in liver disease had properties somewhat different from normal.

Since there are few objective tests for measuring the disturbances of liver disease, Snell's results suggested to us that this test might furnish another index of these disturbances and might parallel changes in the clinical condition of the patients. Accordingly, arterial blood samples were tested on a series of patients being studied under various therapeutic régimes.

## CASE MATERIAL

The subjects comprised 34 patients with clinically diagnosed cirrhosis of the liver, on whom a total of 52 determinations of arterial blood oxygen were made. Twenty of the patients subsequently died, and in 13 of these the diagnosis was established by autopsy. The table presents the results of the tests, together with the patient's age in each case, and brief notes on the diagnosis. Wherever autopsy or liver biopsy was performed, that fact is noted.

## METHODS

Arterial blood was taken under oil from the brachial artery, with the patient recumbent. The blood was mixed with dry potassium oxalate under oil and the oxygen content determined immediately on duplicate 1 c.c. samples with the Van Slyke manometric apparatus. For the oxygen capacity, a further portion of the blood was agitated in room air for 10 minutes, and the determination was made likewise in duplicate. In both procedures the duplicate analyses were required to check within 0.2 vol. per cent.

To obtain a value for the oxygen combined with hemoglobin only, 0.2 vol. per cent was subtracted from the oxygen content and 0.5 vol. per cent from the capacity. Values in the table have been corrected in this manner.

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Research Service (Formerly Research Division for Chronic Diseases), First Division, Welfare Hospital, Department of Hospitals, New York City, and Department of Medicine, College of Physicians and Surgeons, Columbia University, New York City.

between the College of Education and the schools of nursing with a tuberculosis service. Among the students in the College of Education from 1932 to 1937 there was a total of 686 tuberculin reactors, and roentgen-ray film examination both on entrance and graduation revealed one primary parenchymal focus which later resolved and two which proved to have developed clinical disease.

Thus, we have found the tuberculosis problem among the students of nursing in four schools to be much greater than among the students in a College of Education in the same community. In our schools of nursing tuberculosis contracted while in school in the strict sense of the word has resulted in a number of girls discontinuing their training. It has caused much mental anguish among students and their relatives; it has caused long periods of illness; it has already caused death of a few; and it has caused much worry, chagrin, and embarrassment on the part of faculty members who have recognized the problem and feel a strong sense of responsibility for the health of the students of nursing.

A solution of this serious problem is of utmost importance and has been discussed by those who are desirous of eliminating this hazard to nurses in various parts of the world. Such factors as age, tuberculin reaction before entering the school of nursing, dosage of tubercle bacilli, and working hours have been considered important, but our experience has led us to believe that these factors have little to do either with causing the problem or solving it. Several workers have suggested the administration of BCG as the solution of this problem, and some have attempted it. Among 287 student nurses who became reactors following the administration of BCG Heimbeck found that eight later developed what he considered evidence of tuberculosis and one died. Among 107 others to whom he administered BCG, but who did not become reactors soon after, 22 developed what he reports as disease, and two died. Obviously, therefore, BCG did not prove a complete solution of this problem.

In our opinion there is only one true solution available at present, namely, the employment of a technic which will provide a barrier so efficient as to prevent the transmission of tubercle bacilli from patient to student. With this in mind two of our hospitals are already making serious attempts to prevent tubercle bacilli from entering the bodies of our students, both reactors and non-reactors to tuberculin. All members of the hospital personnel are examined adequately and periodically, in order to prevent our students from becoming infected by any person employed in the hospital. Patients entering all departments are examined for tuberculosis in contagious form, in order to avoid exposure of our students to unsuspected cases of tuberculosis. Each of these hospitals now has a tuberculosis service where rigid contagious disease technic is being practiced. If the technic now in use is not found entirely adequate, it must be intensified to such a degree as to solve our problem.

## Summary of Measurements of Arterial Oxygen Saturation in 34 Patients with Cirrhosis of Liver

Patient No.	Age	Sex	O <sub>2</sub> Cont. Vol. %	O <sub>2</sub> Cap'y Vol. %	O <sub>2</sub> Sat'n %	Clinical Notes
1	62	M	16.7	17.6	95	Cirrhosis with massive ascites. Subsequently improved.
2	55	M	17.1	18.6	92	Moderately severe cirrhosis. Also emphysema and bronchitis.
			18.0	19.3	93.5	5 months later. Slightly improved.
3	41	F	10.4	10.7	97	Severe cirrhosis. Later proved by biopsy.
4	50	M	12.9	13.5	95.5	Cirrhosis plus thrombosis of portal vein. Autopsy.
5	82	M	13.8	15.0	92	Severe cirrhosis with ascites.
			14.3	14.8	96.5	8 months later. Improved.
			14.8	15.5	95.5	2 months later. Ascites-free. Autopsy 1 year later. Cirrhosis plus carcinoma of liver.
6	60	M	16.1	16.7	96.6	Cirrhosis with moderate ascites.
			16.0	17.1	93.5	9 months later. Unchanged.
7	48	M	16.3	16.9	96.5	Cirrhosis with ascites and intraperitoneal hemorrhage.
			14.5	15.5	93.5	6 months later. Also hydrothorax.
			13.1	13.6	96.5	2 months later. Condition poorer. Autopsy—Cirrhosis plus intraperitoneal hemorrhage.
8	39	M	17.4	18.0	96.5	Cirrhosis, club fingers.
9	46	M	17.3	17.8	97	Cirrhosis with recent ascites, tabes dorsalis. Autopsy.
10	63	M	13.0	13.7	95	Laennec's cirrhosis with ascites, and hypertensive disease.
			14.7	15.4	95.5	7 months later. Improved.
11	57	M	19.0	19.7	96.5	Cirrhosis plus thrombosis of portal vein. Autopsy.
12	26	F	14.7	15.2	97	Large fatty liver with early cirrhosis. Biopsy.
13	45	M	16.1	16.7	96.5	Cirrhosis. Rapidly downhill. Autopsy.
14	49	M	9.5	10.1	94	Cirrhosis, bleeding esophageal varices, portal vein thrombosis. Autopsy.
15	54	M	11.8	12.4	95	Cirrhosis. Rapidly failing.
16	60	M	15.9	16.7	95	Cirrhosis with moderate ascites.
			15.7	16.6	94.5	2 months later. Unchanged.
17	40	M	15.9	17.9	89	Cirrhosis of liver, femoral thrombophlebitis, pulmonary infarcts (see text).
			17.7	18.7	94	7 months later. Slightly improved.
			16.3	17.2	95	2 months later.
			16.5	17.1	96.5	3 days later.
			17.4	19.2	90.5	8 months later. Further improved.

become ill from tuberculosis is sufficiently large to make the problem a serious one.

9. In the College of Education 24.8 per cent of the entering students reacted to tuberculin, whereas on graduation 28.5 per cent reacted. In a group of 686 reactors examined only three developed lesions in school which were demonstrated by roentgen-ray film examination.

10. A higher percentage of students reacted to tuberculin after taking a nursing course in a general hospital with no special tuberculosis service than in the College of Education. On the other hand, more students reacted to tuberculin after taking a course of nursing which requires a tuberculosis service than students in general hospitals which do not have such services. Obviously, the increase in percentage of reactors depends upon the amount of contact with contagious cases of tuberculosis.

11. In this entire study we have not seen a single student fall ill from miliary tuberculosis, tuberculous meningitis, or the so-called "infantile" type of tuberculosis.

12. Throughout this study no student developed tuberculosis as a non-reactor to tuberculin.

13. Our period of observation is brief for such a chronic disease. Therefore, we are of the opinion that more of the former students whom we have observed will fall ill from tuberculosis. This statement is based on the fact that annually new cases have been reported.

14. We do not believe that BCG has been proved sufficiently efficacious to solve this serious problem since evidence of tuberculosis has developed among some of the students so treated, as reported by Heimbeck and others.

15. In our opinion there is no method available, except a most rigid contagious disease technic, which provides a barrier and prevents the spread of tubercle bacilli from patient to student.

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2. Forty determinations on 31 patients were above 94 per cent, or within normal limits.

3. Twelve determinations on nine patients were below 94 per cent, the lowest being 89 per cent.

4. Of these nine patients, three had complicating pulmonary disease which adequately explains the anoxia. This group includes all instances of arterial saturation below 92 per cent.

5. The incidence of arterial oxygen unsaturation did not parallel other manifestations of the severity of the liver disease.

The initial observations in this work were made by Dr. James S. Mansfield and Dr. André Cournand, to whom grateful acknowledgment is made.

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It has been stated that acute leukosis rarely occurs after 25 years of age; approximately half of the cases in this series were over 25.

### HEREDITY

In only two instances was there a history suggesting primary blood dyscrasias in other members of the family.

### CLINICAL FEATURES

The most common initial symptoms were in the following order: weakness, bleeding manifestations, anorexia, joint pains, unexplained fever, sore throat and general malaise. In only three instances did infection, and in only two instances did trauma apparently initiate the illness. Six cases were discovered because of bleeding following extraction of teeth or tonsillectomy.

A number of symptoms appeared frequently in the history of patients: weakness was present in 60 per cent, unexplained bleeding in 55 per cent, fever in 52.2 per cent, anorexia in 50 per cent, joint pains and bone pains in 47.5 per cent, vomiting in 32.5 per cent, loss of weight in 27.5 per cent, headache in 25 per cent, sore throat in 22.5 per cent, general malaise in 22.5 per cent, pallor in 20 per cent, glandular enlargement in 17.5 per cent, shortness of breath in 17.5 per cent.

A wide variety of other symptoms occurred either initially or during the course of the illness: frequent micturition and swollen testicles, deafness, abdominal pain, diarrhea, vertigo, visual disturbance, coma, drowsiness, convulsions, chills, palpitation, swelling of the salivary glands, chest pain, painful gums and sore mouth, dysphagia and dysarthria. Bleeding gums, epistaxis, purpura of skin and mucous membranes were the most common manifestations of bleeding; vaginal bleeding, hematuria, hematemesis, hemoptysis and melena occurred in several instances. These symptoms were present in all cell types of the disease.

### PHYSICAL SIGNS

On admission to the Hospital general glandular enlargement was present in 24 cases, or 60 per cent. The cervical glands were more frequently involved than any other group, showing enlargement in 12 cases of lymphoblastic and 13 cases of myeloblastic leukosis. Axillary and inguinal glands were frequently involved.

The distribution and degree of glandular enlargement were essentially the same in all cell types of leukosis.

*The Spleen:* The spleen was slightly or moderately enlarged in 10 cases of lymphoblastic and 12 cases of myeloblastic leukosis, a total of 62.5 per cent. On admission the spleen was not palpable in four cases of lymphoblastic and in 11 cases of myeloblastic type of the disease. The spleen was not always palpable in the monocytoid myeloblastic group. Splenic enlargement could not be correlated with the predominating cell type.

## RESULTS

It will be seen that the mean value of all determinations of arterial oxygen saturation, performed on the bloods of 34 patients, is 95.0 per cent, which is only 0.5 vol. per cent below the normal mean value on 12 normal young men, reported by Dill, Edwards, and Consolazio.<sup>4</sup> However, the mean age of our group is slightly over 50. On a group of healthy men over 60, Dill, Graybiel, Hurtado, and Taquini<sup>3</sup> found an average value of 92.3 per cent. Thus, considering average values for our entire group, no significant abnormalities can be noted.

Analyzing the individual cases, we find that in two determinations the oxygen saturation was below 92 per cent which may be considered unquestionably abnormal. However, both of these occurred in patient 17, who presented a special clinical picture. In addition to cirrhosis of the liver, this patient had a recurrent femoral thrombophlebitis with non-filarial elephantiasis. He had had several pulmonary infarcts. The roentgenograms of his chest showed increased markings in both lower lung fields. He complained of dyspnea on exertion, had clubbed fingers, and his pulmonary ventilation at complete rest was approximately 15 liters per minute. These pulmonary complications would seem to furnish adequate cause for his arterial anoxemia.

Although there is apparently no case in this series of severe arterial oxygen unsaturation due to liver disease, there are several instances in which a slight degree of unsaturation is found, i.e., in the range of 92 per cent to 94 per cent. The table shows that 10 determinations on 8 patients fall within this range. These include patients 2 and 19, who had repeated determinations in this range, and 5, 6, 7, 25, 28, and 34, with a single determination in the low range. However, two of these eight patients had frank pulmonary disease. Patient 2 had moderately severe chronic bronchitis and emphysema; patient 7 had a bilateral hydrothorax at the time his arterial oxygen saturation was low.

There remain, therefore, only seven determinations on six patients in which the arterial oxygen saturation was low and in which this fact cannot be explained by pulmonary disease. It should be noted, moreover, that of these six patients, one (number 5) was a man of 82 years, in whom a value of 92 per cent might not be considered abnormal in view of the findings of Dill et al.<sup>3</sup> on elderly men.

Our data have been analyzed to attempt to relate these few instances of lowered arterial saturation to some other feature of the disease in the patients. The finding is not related to the general severity of the liver disease, for it was not found in any of the seven patients who died of uncomplicated liver disease within three weeks of the test. This group includes patients 13, 15, 18, 26, 27, 32, and 33. Patient 33 deserves special mention because he showed an arterial oxygen saturation of 93.5 per cent early in the course of his illness, and 96.5 per cent later when he was moribund.

*Mucous Membranes:* Swollen and ulcerated gums were present in 14 or 35 per cent of the cases, and showed no predilection for the cell type involved. Massive necrosis of the gum and jaw occurred in several cases.

*Tonsils:* These were markedly enlarged in nine cases and again there was no predilection for any cell type.



FIG. 2. Lymphoblastic leukemia. Leukemic involvement of fourth and fifth lumbar vertebrae; third sacral; ilium; ischium; pubis; hip joints; and the proximal femurs.

*Pallor:* When first seen, 37 of the cases or 92.4 per cent showed a greater or lesser degree of pallor; 67.5 per cent exhibited marked pallor. All types of the leukoses were involved.

*Fever:* Fever was present in every case. In three cases the fever resembled but was not typical of the Murchison-Pell-Ebstein type. All types of fever were encountered. Forty per cent of the cases developed complicat-

Summary of Measurements of Arterial Oxygen Saturation in 34 Patients with Cirrhosis of Liver—*Continued*

Patient No.	Age	Sex	O <sub>2</sub> Cont. Vol. %	O <sub>2</sub> Cap'y Vol. %	O <sub>2</sub> Sat'n %	Clinical Notes
18	52	F	9.8	10.4	94	Cirrhosis. Rapidly downhill. Autopsy.
19	35	F	11.1 12.5	12.1 13.4	92 93.5	Severe cirrhosis with ascites. 1 month later. Slightly improved.
20	63	M	15.8 16.8	16.7 17.8	94.5 94.5	Cirrhosis with recent ascites. 5 months later. Improved.
21	42	M	12.5	12.9	97	Severe cirrhosis. Autopsy.
22	50	M	13.9	14.6	95	Cirrhosis with ascites.
23	49	M	15.9 13.5	16.6 14.3	96 94.5	Cirrhosis with ascites. 9 months later. Less ascites.
24	45	F	18.5	19.4	95.5	Cirrhosis with severe peripheral neuritis.
25	36	F	11.0 11.3	11.9 12.2	92.5 94.5	Severe cirrhosis with ascites. 1 week later. Unchanged.
26	52	F	17.8	18.2	98	Cirrhosis. Moribund.
27	31	F	12.2 16.8	12.7 17.5	96 96	Severe cirrhosis with ascites. 4 months later. Unchanged. Autopsy 2 months later.
28	56	F	11.6	12.4	93.5	Severe cirrhosis with ascites.
29	59	M	13.1	13.7	95.5	Cirrhosis with ascites.
30	53	F	12.7	13.3	95.5	Cirrhosis with ascites, cerebral arterio-sclerosis.
31	53	M	16.3	17.0	96	Cirrhosis, recently improved. Autopsy 1 year later.
32	60	F	9.4	9.7	96.5	Cirrhosis—rapidly failing.
33	38	M	18.9 19.7	20.2 20.4	93.5 96.5	Cirrhosis—rapidly failing. 3 weeks later. Worse. Autopsy.
34	44	M	14.7	15.3	96	Severe cirrhosis with ascites. Autopsy.
Mean	50				95.0	

Likewise, attempts were made to correlate the few instances of arterial oxygen unsaturation with separate clinical features and laboratory tests: with jaundice, with severity of ascites, with peripheral neuritis, with level of serum albumin and bromsulphthalein retention. No correlation could be found with any of these features.

## SUMMARY AND CONCLUSIONS

1. Fifty-two determinations of arterial oxygen saturation were made on 34 patients with cirrhosis of the liver.

the literature of a comparably high incidence of lung changes on roentgen-ray examination.

*Bone Involvement:* That gross bone involvement may occur is illustrated by the presence of demonstrable roentgen-ray lesions of the tibia, femur, lumbar and sacral vertebrae, and pelvic bones in one of our cases. The high incidence of joint pain would suggest the desirability of further roentgen-ray and histologic study of joint tissues. Bone tenderness was a common sign.

*Neurologic Involvement:* This occurred in 22.5 per cent of cases, showed no predilection for the cell type involved and included cranial nerve palsies, evidence of cerebral, spinal cord and peripheral nerve lesions. Drowsiness, convulsions, and coma occurred in several cases.

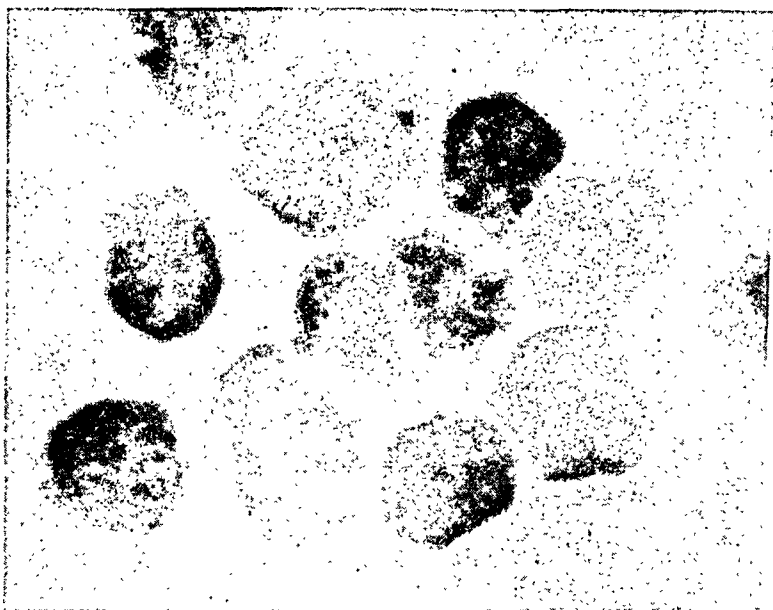


FIG. 4. Lymphoblastic Leukosis. Lymphoblasts in the peripheral blood. Note mitotic figures and Klein-Gumprecht shadows.

*Miscellaneous Signs Noted:* These included obstructive jaundice in two cases, extreme cyanosis, cardiac enlargement, Mickulicz' syndrome, and a tumor attached to the ribs.

*Laboratory Findings:* Elevated basal metabolic rates varied from plus 22 to plus 58 per cent. The blood non-protein nitrogen content was elevated in several cases. The highest value of 87 mg. per cent was associated with a uric acid of 20.2 mg. per cent, and at postmortem examination there was massive leukoblastic invasion of the kidney; the uric acid was elevated in 69 per cent of cases estimated.

Blood cultures, made from 14 cases, were sterile in every instance. Hematuria was present in 26 per cent. Fever could explain the other features found on urinalysis.

# A STUDY OF THE ACUTE LEUKOSES\*

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MANY contributions have been made to the study of acute leukosis. Confusion still characterizes many features of this disease. We wish to present a clinico-pathologic study of 40 cases of acute leukosis observed in the Royal Victoria Hospital of Montreal in the past 20 years. We hope that this study will prove helpful in reëvaluating the wide diversity of opinions expressed.

We would define acute leukosis as a fatal disease of short duration, characterized by an untoward proliferation of primitive leukocytes in the hemato-poietic tissue of the bone-marrow, lymph nodes, and spleen, with delivery of these cells to the peripheral blood in greater or lesser numbers. Infiltrations or metaplasia or both commonly appear in a wide variety of tissues and organs.

Hughes Bennett and Rudolph Virchow<sup>38</sup> first described leukemia in 1845. Virchow's original differentiation of lymphocytic leukocythemia and splenic leukocythemia is still widely applied, even in the classification of the acute leukoses.

Since the first case of acute leukosis was described by Von Friedriech<sup>32</sup> in 1857, further subdivision has been made on the basis of cell morphology. Some have attempted to elaborate a clinical picture peculiar to the cell type involved. The data available in this series of cases do not permit this differentiation.

## INCIDENCE

In the past 20 years the incidence of acute leukosis was one case in 5960 admissions; 21 cases or 52.5 per cent were myeloblastic, 14 cases or 35 per cent were lymphoblastic, and 5 cases or 12.5 per cent were classified as monocytoïd myeloblastic leukemia.

It is possible that the latter five cases were monoblastic. After a careful review of the material available, we were still unable to establish final conclusions in this matter. Although we have utilized supravital and other differential technics, we have failed to discover a single case of monoblastic leukosis in the past several years. As in the literature,<sup>49</sup> myeloblastic leukosis was the most common type.

In contradistinction to the usually reported greater incidence in males,<sup>20, 37, 47, 49</sup> 21 cases were females, and 19 were males.

Again in contradistinction to other reports,<sup>20, 47, 48</sup> the cases were almost equally distributed in the first four decades of life. After 40 the incidence decreased. The youngest case was two years of age and the oldest was 75.

\* Read before the General Session of the American College of Physicians in Cleveland, Ohio, April 2, 1940.

blood of the lymphoblastic leukoses. There was one case of lymphoblastic leukosarcoma.

Button or punch bone-marrow biopsy invariably showed the presence of a significant number of the responsible cell type.

*Bleeding and Clotting Phenomena:* In the three cases tested the blood prothrombin concentration was significantly decreased. In 15 cases the bleeding time was slightly to greatly prolonged. The clotting time was delayed in a number of instances. Rumple-Leeds test when performed was usually positive.

#### EFFECT OF THERAPY

In general, transfusions had no effect on the rapid progress of the anemia. In only a few instances was there any appreciable beneficial effect and this lasted only a few days. Transfusions had no definite effect on the white cell picture.

*Deep Roentgen-ray Therapy:* In several instances this was followed by a more marked thrombocytopenia and the initial appearance of bleeding. Roentgen-ray therapy was used in nine cases. In two instances the total leukocytes increased after therapy, and in two instances there was a marked increase of leukoblasts. In several instances roentgen-ray therapy was followed by a drop in the count, only to rise again several days after the discontinuation of the treatment. In not one case was there any lasting clinical or hematological benefit following roentgen-ray therapy. In several instances we believe this treatment hastened the lethal course of the disease. Radiation sickness occurred frequently after roentgen-ray therapy. Fowler's solution, benzol, and all other forms of therapy used had no appreciable effect.

#### PATHOLOGY

Postmortem studies were made in three cases of monocytoid myeloblastic, four cases of lymphoblastic, and eight cases of myeloblastic leukosis.

Grossly, regardless of the cell strain involved, hepatomegaly, splenomegaly, general glandular enlargement, hyperplastic bone-marrow and hemorrhagic manifestations were present in every case. In two cases enlargement of the retroperitoneal glands was greater than the glandular enlargement elsewhere. Diffuse hyperplastic metaplasia was present in the bone-marrow, lymph nodes, spleen and liver, in every case autopsied.

Leukemic infiltration of a wide variety of tissues and organs was the rule. The responsible cell strain in no way determined the tissues involved. The degree of infiltration in any given organ varied from case to case. Leukoblasts almost invariably jammed the radicles of the portal veins, the portal and periportal areas, and in two instances formed gross tumor nodules in the liver. Massive infiltration of the kidneys, sufficient to produce renal insufficiency, was present in one lymphoblastic and two myeloblastic cases. In two cases the enlargement of the spleen and liver was so marked (e.g.,

*The Liver:* The liver was enlarged in 10 cases of lymphoblastic and nine cases of myeloblastic leukemia, a total of 47.5 per cent. It was not enlarged in four lymphoblastic and in 13 myeloblastic cases. The liver was not always enlarged in the monocytoid myeloblastic group. It will be noted that the liver was more frequently enlarged in the lymphoblastic than in the myeloblastic leukoses.

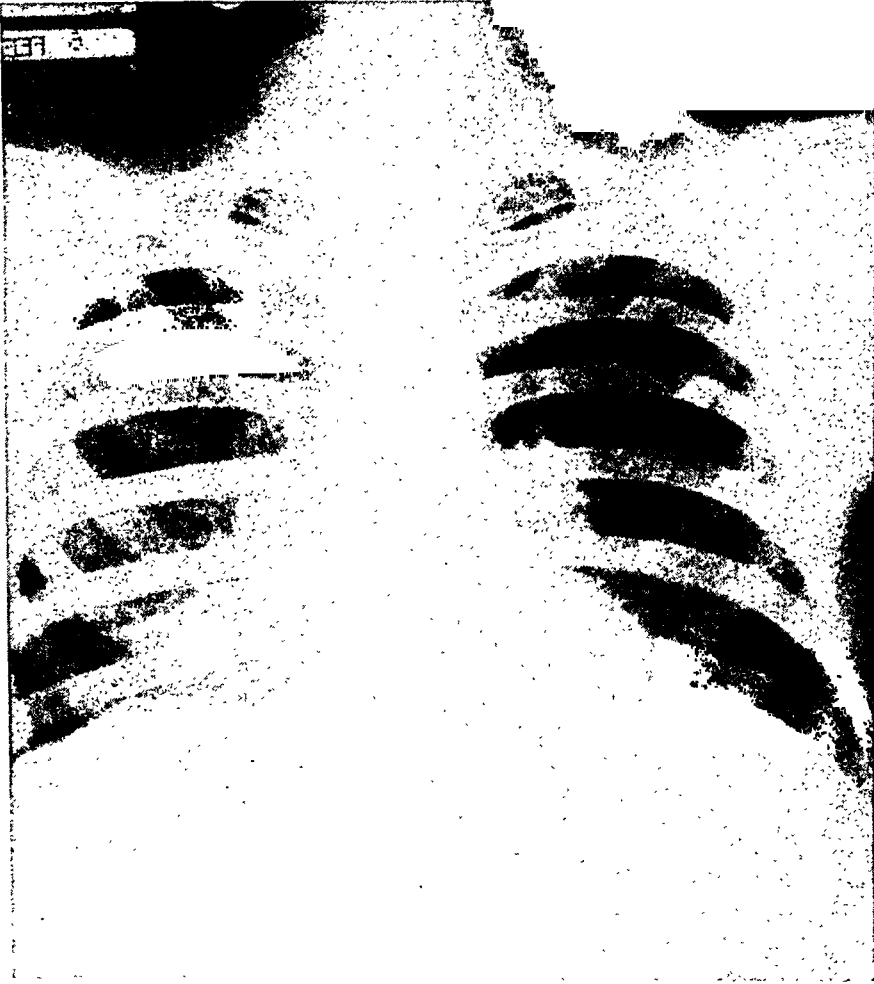


FIG. 1. Lymphoblastic leukemia. Leukemic involvement of mediastinum and lung. Bilateral hilar shadows with increased markings of lower right lung.

*Bleeding Phenomena:* During hospitalization bleeding occurred from one or several sources in the majority of cases of all cell types. The most common clinical sites of bleeding were the skin, mucous membranes, and retinae. Severe generalized hemorrhagic manifestations were not infrequent. Signs of visceral hemorrhage were present in many instances.

*Skin Lesions:* One case of lymphoblastic and four cases of myeloblastic leukemia showed leukemia cutis. The type of lesion differed in every instance.



nature of the infiltrative process in this disease, symptoms and signs may appear referable to disturbed physiology in almost any organ in the body. Recently a number of authors have referred to certain aspects of this subject.<sup>1-10, 12-15, 17-19, 21-24, 26-28, 30-36, 39-46, 49-51</sup> When present, bleeding into the skin, or from mucous membranes, fever, diseased gums or pharynx, general glandular enlargement, a large liver or a large spleen suggest a thorough hematologic observation. The latter includes, in addition to regular routine studies, supravital studies, marrow biopsy, gland juice and gland core studies, and adrenalin contraction of the spleen. The grave anemia, thrombocytopenia, the white cell count and the differential count, as well as the study of the clotting mechanism, were all important in arriving at an accurate diagnosis. Greatest difficulty is encountered in the leukopenic form of the disease. In spite of the more accurate means available to investigate these cases, time, patience, and repeated study are often necessary before a definite diagnosis can be made. This is even more true in the leukopenic stage of the disease. The appearance of a few relatively mature cells in the peripheral blood aids greatly in establishing a diagnosis.

#### DIFFERENTIAL DIAGNOSIS

Leukemoid states should always be considered in the differential diagnosis of the acute leukosis. The disease must be differentiated from neoplasms with bone marrow metastases, severe infections, malignant neutropenia, pneumonia, tuberculosis, pertussis, rheumatic fever, infectious mononucleosis, aplastic anemia, thrombocytopenic purpura, scurvy, lymphoblastoma, some primary anemias of children, and last but not least from an acute exacerbation of a chronic leukosis.

#### COMMENT

In this study of the acute leukoses, including 15 autopsies, we have been unable to correlate the history, clinical signs, laboratory findings, or gross pathology with a specific cell type, in contradistinction to the reports of others.<sup>20, 30</sup>

Surface evidences of bleeding usually indicated greater hemorrhages into internal organs. All lymphatic glands were extensively involved, regardless of the cell type of the disease.

Occasionally a full blown disease was discovered after a trivial operation (e.g., tonsillectomy), a minor infection (e.g., an infected finger), or a moderate injury (e.g., blow on chest). We agree with others that there is insufficient evidence to conclude that these factors played any etiological rôle.<sup>16, 52</sup> We were impressed with the pan-systemic invasion and reaction. No true remission was observed in this group of cases.

Anemia was always present, and was generally very marked. The red blood cells showed degenerative and regenerative evidences. Nucleated red blood cells were abundant, reticulocytosis was prominent, and hemolytic ten-

ing infections. Broncho-pneumonia was the most common and occurred in five cases.

*Weight Loss:* Weight loss occurred in 62.5 per cent of the cases.

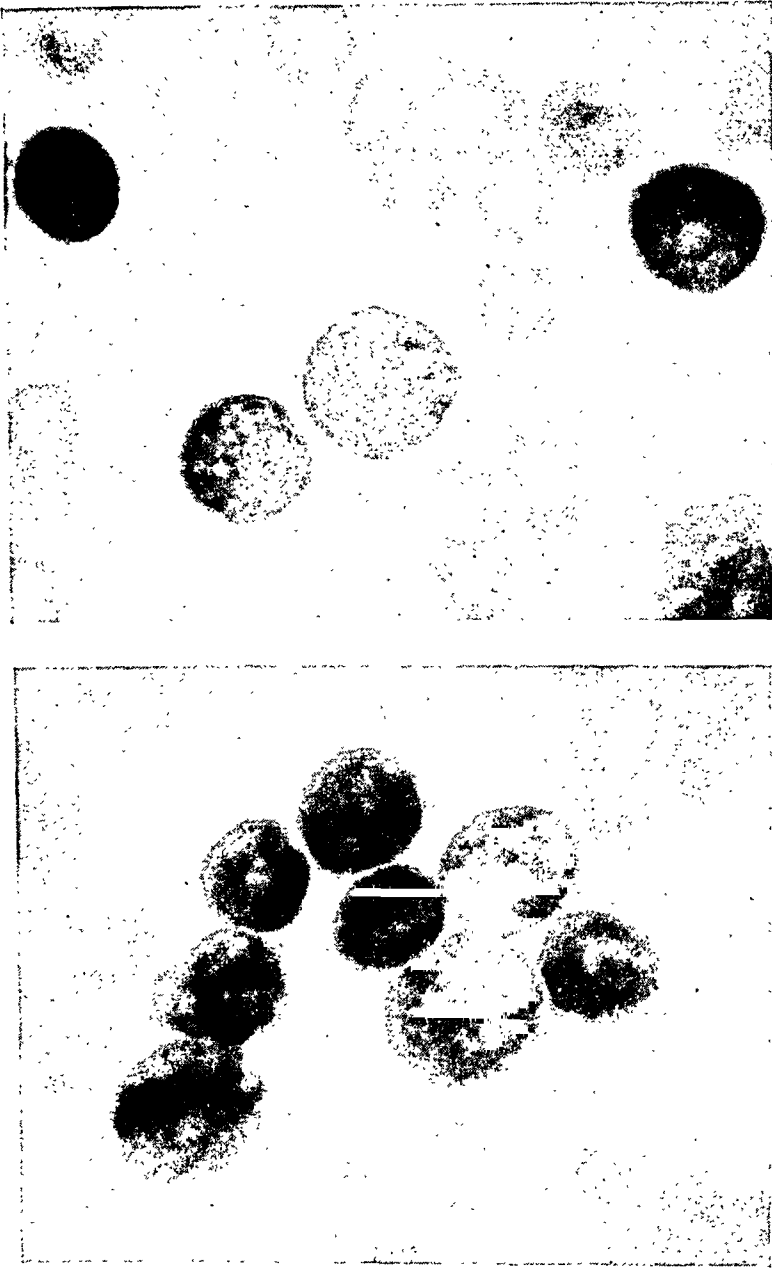


FIG. 3. Micromyeloblastic Leukosis. (a) *Above:* Micromyeloblasts in the peripheral blood. (b) *Below:* Cluster of micromyeloblasts in tissue aspirated after sternal bone marrow puncture.

*Roentgen-rays of Lungs:* Roentgen-rays of the chest were made in 22 cases; 15 showed thickened lung roots, and in 4 instances the lung parenchyma showed diffuse infiltration. We have been unable to find mention in

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*Duration of the Disease:* The average duration was 10.2 weeks. The shortest duration was nine days; it occurred in a boy slightly over three years of age. The longest duration, eight and one-half months, was observed in a man aged 41 whose illness began with Brill's disease. The diagnosis of acute lymphoblastic leukosis was made three weeks before death. During the past 10 years there were twice as many cases of acute leukosis found in this hospital as were detected during the previous 15 years.

*Mode of Death:* We were particularly impressed with the mode of death in 28 or 70 per cent of the cases which was characterized by extreme weakness, circulatory collapse, rapid and labored respirations. Complicating infection was present in 20 per cent of the cases at the time of death. Terminal hemorrhage contributed to the circulatory collapse and death in eight cases, or 20 per cent. Five of these cases had subdural, subarachnoid, or cerebral hemorrhage.

*Course:* The course was universally downhill regardless of the treatment. Six cases developed coma. At least two cases became progressively worse after roentgen-ray treatment. All cases under observation for more than two weeks showed progressive enlargement of lymph glands, spleen and liver. Pallor and anemia increased with passage of time.

#### HEMATOLOGY

On admission anemia was present in 39 or 97.5 per cent of cases. Almost one-third of the cases showed a moderate degree of anemia, i.e., between two and three million red blood cells and 40 to 60 per cent hemoglobin. Two-thirds showed a marked anemia, i.e., below two million red blood cells and below 40 per cent hemoglobin. In the majority of cases, the anemia was normochromic and normocytic; in a number of instances it was hyperchromic and macrocytic and in others hypochromic and microcytic. Nucleated red blood cells were present in 69.5 per cent and reticulocytosis in 57.5 per cent. As judged by the Van den Bergh reaction evidence of hemolysis was present in eight of the 10 cases studied. Thrombocytopenia was present in 84.4 per cent of the cases. In general the thrombocytopenia became more marked as the disease progressed.

The initial total white cell count was normal in six cases, leukopenic in two cases, and leukocythemic in 32 cases. The leukocythemic bloods varied from slightly above normal to 363,000 leukocytes. Spontaneous changes from a leukocythemic to a leukopenic phase occurred in two cases. In one case the white blood cell count rose spontaneously from 900 to 375,000. The other leukopenic case remained leukopenic. Most of the leukocythemic cases showed a tendency to progressive increase of the white blood cell count.

All leukoblasts were oxydase negative.

Several cases of myeloblastic leukosis were micromyeloblastic and usually careful search revealed the presence of occasional myelocytes. Auer bodies were present in the leukoblasts in two cases of the myeloblastic series and in one of the monocytoid cases. An occasional myelocyte was present in the

# CASE REPORTS

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## HEREDITARY ANGIONEUROTIC EDEMA \*

By A. H. FINEMAN, M.D., F.A.C.P., *New York, N. Y.*

ANGIONEUROTIC edema is usually regarded as a peculiar and interesting condition, appearing suddenly as a subcutaneous, localized swelling on one or more parts of the body and disappearing gradually without leaving any discernible evidence of the reaction. It was first described in detail by Quincke,<sup>1</sup> in 1882, as "an acute circumscribed edema of the skin" to differentiate it from the well-known superficial whealing of urticaria, and given the name angioneurotic edema by Strübing,<sup>2</sup> three years later. It was believed by both these authors that the underlying mechanism responsible for this condition was a vasomotor disturbance of the blood vessels (angioneurosis) of the subcutaneous and submucosal tissues giving rise to increased capillary permeability and edema, but the factors that regulated and controlled this mechanism were not understood. In the past two decades this condition has come to be looked upon as a manifestation of allergy. Evidence has been accumulated to support the view that protein hypersensitiveness plays an important rôle in the causation of this disorder. Many reports of large series of cases have been published wherein protein skin tests, in some measure, have proved to be of diagnostic aid in determining the etiologic factors and yet it is in this type of allergy that the least satisfactory results are obtained.

Angioneurotic edema may be classified into three clinical types: (1) the acute or transient type, (2) the chronic or recurrent, and (3) the familial or hereditary type, with which this article is particularly concerned.

The *acute* type is characterized by localized, pale, indurated swellings surrounded by erythema varying in size and shape and occurring most frequently on the face, eyelids, lips and extremities, less often on other parts of the body. Rarely are the mucous membranes of the pharynx, glottis and larynx involved. It usually affects young adults, more often females than males. As a rule there is a history of only one or two attacks without subsequent recurrence. Protein skin tests sometimes help in determining the etiology but frequently the condition disappears without any known cause. A positive family history of allergy is elicited in only a small per cent of cases. In this type the prognosis is good.

The *chronic* type differs from the aforementioned in that attacks occur more frequently and the illness extends over a longer period of time. The areas involved are usually the same except for a greater tendency to affect the throat and larynx. Edema of the latter may give rise to alarming symptoms but rarely terminates fatally. Protein skin tests are more apt to be positive, and yet, here too an appreciable number of cases are found to be refractory to the great variety of allergens commonly used. Foci of infection, gastrointestinal disorders, psychogenic and endocrine disturbances have been demonstrated to be of etiologic

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From the Allergy Clinic, Sydenham Hospital.

myeloblastic leukosis with a spleen of 1500 gm., and liver of 3030 gm.) that the possibility of a preëxisting chronic leukosis was suggested.

Extensive and diffuse hemorrhage involved in order of frequency the skin, mucous membranes, pericardium, stomach, retinae, peritoneum, renal tissue, brain and lungs. Although purpura of the skin was the most common single site of hemorrhage, simultaneous bleeding in a number of the viscera was far more frequent and extensive.

Hemorrhagic infarcts of the spleen, bilateral hydrothorax and broncho-pneumonia were each present in 25 per cent of the cases. Secondary infections were present in isolated instances. In several cases there was myocardial injury, due to fatty degeneration, leukoblastic infiltration or fragmentation of muscle fibers. Exudative ulcerative stomatitis was present in one case of the monocytoid variety.

We were particularly impressed with the presence of non-inflammatory pulmonary edema in those cases without pulmonary infection, and with the degree of pulmonary edema in those cases developing pneumonia.

Frequently, leukocytes occluded the lumina of many small blood vessels. Perivascular hemorrhage often occurred in the vicinity of these vessels.

The hematopoietic tissues exhibited several features of interest pertinent to the mechanism of the anemia:

1. In several cases large areas of comparatively normal bone-marrow were found in which leukemic cell hyperplasia was minimal, yet the anemia was severe in these cases.

2. Evidence of increased red cell destruction was found in the bone-marrow, spleen and liver of every case. Internal hemorrhage may have partially conditioned this finding in some instances. In several cases, however, hemorrhage was negligible and yet there was a hyperplasia of clasmato-cytes and Kupffer cells, which were loaded with pigment, red cell fragments, and whole red blood cells.

The exudate of the pneumonias consisted predominantly of leukemic cells. Purpura of the skin was invariably associated with much more extensive bleeding into the viscera.

The blood picture rarely indicated the degree or distribution of visceral infiltration. Frequently the tissue infiltration was more striking than would be anticipated from the blood picture and occasionally vice versa. In two instances a rapid decrease of the peripheral leukocyte count was associated with symptoms due to sudden deposition of leukemic cells in the viscera.

On study of histological sections it was frequently impossible to differentiate the particular cell strain involved, nor were there pathological features characteristic of a particular cell type.

#### DIAGNOSIS

A careful clinical history and a thorough physical examination are of great importance in establishing the diagnosis. Because of the widespread

Brown<sup>18</sup> omit it from their statistical studies on urticaria and angioneurotic edema. Because of the rarity of this condition and the serious aspects associated therewith another family is added to the literature with a detailed report of two of its six afflicted members.

#### CASE REPORTS

*Case 1.* R. McC., a 19-year-old girl with a seven-year history of localized swellings on various parts of the body, was perfectly well up to 12 years of age, at which time she first observed swellings of the hands, feet and face lasting 12 to 24 hours and recurring every few months, but in no way incapacitating her. In the last two years the attacks became more frequent and more severe and would occasionally affect the face so that both eyes would be completely closed for a few days. At no time was there hoarseness, difficulty in swallowing, choking sensations or swelling of the tongue. Seldom would nausea, vomiting or abdominal pain accompany the illness.

There was no relation of the edema to the menstrual cycle or seasons of the year, nor was there any history of attacks following exposure to cold or heat. Emotional excitement, however, would occasionally precipitate an attack. It is interesting to note that a tonsillectomy was performed about the time of onset of the trouble. Diet, infections, drugs or contactants could not account for its appearance. The mother reports that protein skin tests were done with negative results. There was no history of urticaria, asthma, hay fever, eczema or migraine in the patient or in any known member of the family. All other data are irrelevant except for the familial history of angioneurotic edema. The mother, maternal grandmother and great-grandmother suffered with the same condition and one brother and sister were similarly affected. Since no reliable account concerning the other relatives was obtainable a genealogic table was not included in this report.

On January 22, 1936, the patient noticed a slight swelling of the right side of the neck and consulted a dentist. The following day she felt better, the swelling had somewhat subsided and at 6 p.m. she went to work in a cabaret restaurant where she was employed as a dancer and observed that the swelling was gradually becoming larger. Being much concerned she left earlier than usual and returned home at 9 o'clock, at which time both sides of the neck were involved. Within five minutes she gasped for air, rushed out to the street and pointed to her throat as the site of the trouble. Her face became swollen and cyanotic, the dyspnea more extreme and she was rushed to the hospital only two blocks away where she died while being carried to the emergency room. The intern who responded immediately to the call found her pulseless and frothing at the mouth and administered an intracardiac injection of epinephrine hydrochloride (1-1000), 1 c.c., without effect. She had died of asphyxia before tracheotomy could be performed.

Examination shortly after death revealed a milky-white indurated edema of half of the lower lip and extreme edema of the soft palate, uvula and pharyngeal muscles of the same serous appearance. The glottis was completely obstructed and would barely permit the passage of a fine probe under pressure. The tongue, cheeks, hard palate and epiglottis were not involved. The larynx was not examined and no autopsy obtained.

*Case 2.* Mrs. McC., 47 years of age, mother of the patient just described, was admitted to the allergy clinic 10 days later. She gave a history of angioneurotic edema of the upper and lower extremities and face since the age of nine with attacks occurring every few months in the early years and later more frequently. The throat was never involved. Only occasionally did she have vomiting and a bloated feeling in the abdomen.

Physical examination was essentially negative. A complete series of protein skin tests with the scratch and intradermal methods revealed negative results. She

dencies were common. Thrombocytopenia was a constant feature. Prothrombin concentration was reduced in the cases studied. Immature white blood cells were constantly present. There were very few leukopenic cases in this series.

Acute leukosis is a disorder of all hematopoietic tissue in which white cells, platelets, red blood cells, hemoglobin formation, the clotting mechanism, and the physiology of internal organs are affected. In a number of instances the clinical and pathologic data (i.e., the increased indirect bilirubin, the failure of multiple repeated transfusions to improve the anemia, the presence of an abundance of healthy marrow in several cases, and the almost universal histologic evidence of increased red cell destruction) suggested that a hemolytic process rather than myelophthisis may have played the dominant rôle in the production of the anemia.<sup>29</sup> Inasmuch as the etiology is unknown, we would support the hypothesis that a maturation factor abnormality may eventually explain the pathogenesis of acute leukosis.<sup>11</sup>

### CONCLUSIONS

1. We do not believe that there is a clinico-pathologic picture which is characteristic of the cell type involved in acute leukoses.
2. No therapeutic measure influenced the course of the disease.

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and larynx become affected. Depending on the severity of the attack one or more of the following measures should be employed: (1) administration of epinephrine hydrochloride (1:1000) subcutaneously or intravenously and if necessary around the periphery of the pharyngeal swelling, (2) passage of a fairly firm rubber tracheal catheter beyond the edematous area and (3) tracheotomy as a last resort in extreme cases. Time is an important factor, and in some instances minutes weigh the balance between life and death. Patients should be warned of these dangers and strongly urged to seek medical care at the slightest suspicion of swelling of the throat. They should also be advised to carry with them, at all times, a nebulizer containing epinephrine hydrochloride (1:100) and a hypodermic syringe of epinephrine (1:1000) for self-administration.

#### COMMENT

Because of the serious consequences attached to hereditary angioneurotic edema this condition must be recognized and differentiated clinically from the relatively benign non-familial variety commonly seen. This can easily be accomplished by careful questioning on the part of the physician as to whether or not other members of the family and their antecedents have been afflicted with the same disorder. One must think not only of urticaria, asthma, hay fever and the other allergies when dealing with angioneurotic edema but must always bear in mind the possibility of that unusual type which is transmitted from generation to generation to the exclusion of the other allergies. In this variety sensitization to foods, inhalants, drugs and bacteria does not seem to play an etiologic rôle but some evidence points to the possibility that physical agents and emotional stimuli act as exciting factors. In the two cases herein reported trauma was believed to have been responsible for an occasional attack and no other history could be elicited which would throw light on its etiology. Whatever the agent may be, it is reasonable to assume that it is the same for all affected members of a family. In this connection it should be noted that hay fever, in some instances, occurs in many members of a family and through several generations, in the absence of all other manifestations of allergy and due to specific hypersensitiveness to the same pollen antigen. Such a circumstance, to be sure, is not common and is explained on the basis of an unusually strong hereditary factor. It is generally believed that the more complete the inheritance, the greater the incidence of the same type of allergy; and so it may be with hereditary angioneurotic edema where the inheritance factor is most complete but where the causative agent is not definitely known. In this variety the edema is extensive and severe, with a predilection for the glottis and larynx and frequently causes death from asphyxia, while in the non-familial variety, where the hereditary influence is incomplete and at times apparently absent, the edema assumes a much milder course and rarely endangers the life of the patient.

Histamine has been recently employed with some success in the treatment of non-familial angioneurotic edema and is worthy of trial in the hereditary type.

#### SUMMARY

Hereditary angioneurotic edema is discussed and differentiated from the acute and chronic varieties commonly seen. A family of six affected members in four generations is added to the literature with a report of two cases, one terminating fatally from edema of the glottis.

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family medical history was unimportant. In the past he had been free from major illnesses, with the exception of an attack of polyarthrititis during childhood. This was thought to have been rheumatic fever, and bed rest had been enforced for eight weeks. From then on he had had no recurrence of the joint trouble, and no return of fever.

Forty-eight hours before being seen, the patient had become ill with headache, backache, and chilly sensations; elevation of temperature followed shortly, and he lost all desire for food. There were no cardio-respiratory or urinary symptoms and, with the exception of the anorexia, no gastrointestinal complaints. Sweating had occurred at intervals, and at times had been profuse. There was no pain in the joints. Until the onset of this illness, he had believed himself to be in good health.

Physical examination showed a robust young man who was not strikingly ill. The skin was warm and moist. The eyes, ears, and nose were negative to examination. The tongue was coated, and the pharynx slightly injected. There was a moderate amount of lymphoid tissue on the posterior pharyngeal wall. The neck was negative except for two moderately oversized nodes in the left anterior cervical chain. The lungs and heart showed no abnormalities. The heart rate was 90 to the minute, and the blood pressure was 132 mm. Hg systolic and 86 diastolic. Examination of the abdomen gave negative results. The extremities and reflexes were normal.

The temperature taken orally was 100.8° F. The white blood cells numbered 8,400, the red cells 4,560,000, and the hemoglobin was 84 per cent by the Sahli method. A differential count showed the white cells to be 58 per cent polymorphonuclear neutrophils, 40 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophiles. Examination of the urine was negative.

The patient was thought to have grippe with pharyngitis, and the usual symptomatic measures were prescribed. Though during the next two days he improved symptomatically, his evening temperature continued at elevations of 101.0° to 102.0° F. At this time it was thought that the pharyngeal injection had increased, and he was given sulphanilamide, 45 grains daily, for the next three days. This, however, had no effect on the fever, thermometer readings continuing to fluctuate between 99.0° and 100.0° F. in the morning, and 101.5° and 103.0° F. in the evening. The drug was discontinued at the end of the three day period because of nausea and vertigo.

On the ninth day of the disease, agglutination tests for typhoid, paratyphoid A and B, melitensis, and tularemia were negative. An intradermal injection of a 1-100 dilution of *Brucella abortus* antigen failed to give a reaction. On the eleventh day another intradermal injection of a 1-5 dilution of the same material gave identical results. On the thirteenth day of the disease, another set of agglutination tests for typhoid, paratyphoid A and B, melitensis, and tularemia, performed in two different laboratories, gave negative results. Undiluted *Brucella abortus* antigen produced no reaction in 48 hours after injection within the skin. A blood culture was sterile, and a film of the chest negative. Several repetitions of blood counts and urine examinations revealed no essential changes from those originally done. Throughout a two-week period, the patient remained remarkably free of symptoms, with the exception of anorexia and sweats. His temperature continued at essentially the same level, readings in the morning being 99.0° F. to 100.0° F., and those in the evening being 101.5° F. to 103.0° F. Daily physical examinations failed to reveal any significant change.

On the fifteenth day of the disease, it was decided to give him another but more intense course of sulphanilamide. Accordingly, on the first day he received 60 grains of the drug, on the second day 80 grains, on the third day 90 grains, on the fourth day 80 grains, and on the fifth day 60 grains. Thereafter sulphanilamide was given, 45 grains daily for four days, and then stopped entirely. On the third day of drug administration, the nail beds and lips were cyanotic. On the fourth day of therapy, the skin at the site of the three previously negative intradermal tests showed the circumscribed inflammation of a positive reaction. The degree of reaction, more-

significance. A positive family history of allergy is more often elicited and a history of other forms of allergy in the patient is more frequently obtained. Here, too, the prognosis is good.

The *hereditary* type is classified separately because it occurs in many members of a family and is transmitted from generation to generation, differing in this respect from the nonfamilial types just described. The line of inheritance seems to be direct with no skipping and reappearing and is apparently governed by a dominant Mendelian characteristic. Members not involved are less liable to transmit the disease. It occurs more frequently in males than in females and has its onset at any age. Once developed the tendency to recur remains throughout life. In some instances the same areas are involved but generally different parts of the body are affected. It is in this variety that edema of the glottis and larynx frequently occurs and terminates fatally. Osler,<sup>8</sup> who first emphasized the hereditary aspect of this condition, cites a family of 36 individuals through five generations in which 22 were affected, with one or possibly two deaths from sudden "edema glottidis." Ensor<sup>4</sup> reports a family of 80 persons in three generations with 33 afflicted members of whom 12 died of suffocation. Crowder and Crowder<sup>5</sup> in an article entitled "Five Generations of Angioneurotic Edema" published a family of 64 members in which 28 were affected and 15 died from the acute form of the disease. Fritz<sup>6</sup> cites eight afflicted members with five deaths and Blumer<sup>7</sup> reports six with four fatalities. Bulloch<sup>8</sup> in an analysis of 26 published reports assembled 170 cases occurring in families in from two to seven generations and in 36 instances (21.1 per cent) death occurred from edema of the glottis, indicating the high mortality rate of this condition. More recently Dunlap and Lemon<sup>9</sup> tabulated 21 families from the literature and added one of their own consisting of 24 members, six of whom died suddenly, two of undoubted glottic edema. From this brief review one is impressed with the seriousness of this type of edema as contrasted with the non-familial variety previously described.

The hereditary type is at times associated with visceral manifestations characterized by nausea, vomiting, abdominal colic and diarrhea which may simulate an acute surgical abdomen but which can usually be differentiated from it by the history of subcutaneous swellings on various parts of the body. In the absence of this history, however, the diagnosis is more difficult and operations have been performed for manifestations which later proved to be localized edema of the viscera.

In the reported cases where protein skin tests were done with some of the common allergens the results were invariably negative. In one member of the family herein discussed (case 2) a complete series of skin tests was performed with negative results. Keidel,<sup>10</sup> however, obtained a markedly positive reaction with an autogenous vaccine of *B. coli* obtained from the stool of a young girl with this disease, but the significance of the reaction is equivocal. The personal and family history in this variety does not usually reveal the presence of any other type of allergy.

Fortunately this type of edema is extremely rare. Rowe,<sup>11</sup> Tuft,<sup>12</sup> Hansel<sup>13</sup> and Bray<sup>14</sup> in discussing it quote instances from the literature but apparently have had no personal experience with it. Rackemann<sup>15</sup> also mentions this condition but reports no observations from his own clinic or practice and considers the incidence of such cases extremely rare. Menagh,<sup>16</sup> Fink and Gay,<sup>17</sup> and

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FATAL "CONSTRUCTIVE" PERICARDITIS DUE TO ISOLATED  
SUPPURATIVE PERICARDITIS THE RESULT OF  
INFECTED ABORTION; CASE REPORT\*

By SIMON KOLETSKY, M.D., and ROBERT E. BROWNLEE, M.D.,  
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THE object of this report is to describe a case of isolated suppurative pericarditis complicating a postabortive thrombophlebitis of the pelvic veins. Only one similar instance of suppurative pericarditis following an abortion has been found in a survey of the literature.<sup>1</sup> The pericarditis was evidently embolic in origin and developed about two weeks after the abortion. The patient then rapidly developed the symptoms of severe cardiac constriction† and died in circulatory failure within a period of eight weeks. An autopsy revealed extensive organization of the pericarditis and the formation of thick and rigid pericardial scar tissue.

## CASE REPORT

*Clinical History:* B. K., a white housewife, 28 years of age and the mother of three children, was admitted to University Hospitals on September 18, 1938 with complaints of severe dyspnea and edema of the lower extremities. Nine weeks before admission an allegedly criminal abortion was performed when she was one month pregnant. Following this procedure she had profuse vaginal bleeding for several days and then developed chills and fever together with a foul vaginal discharge. These subsided completely within two weeks but she failed to improve and remained in bed most of the time because of weakness and dyspnea. There was no abdominal pain. Five weeks before admission she began to complain of epigastric distress, nausea and frequent vomiting. Two weeks before admission she noticed swelling of the ankles for the first time. The shortness of breath and edema became progressively worse and she entered the hospital.

Her health prior to the present illness had been excellent.

*Physical Examination:* The temperature was 37.5° C., pulse 105-130, respirations 36 and blood pressure 100 mm. of Hg systolic and 80 diastolic. The patient was a well developed woman propped up in bed and showing extreme dyspnea. Although

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† The term constrictive is employed because of its widespread use in the literature. The term applies only in its figurative sense of holding fast or gripping, not necessarily in the sense of drawing together or rendering narrower or smaller. The lesion constrains the heart's diastolic expansion, but does not truly reduce the size of the heart in its systolic phase nor in its weight.

was given elimination and trial diets without beneficial effect. During 18 months' observation she had 13 or 14 attacks, each lasting two or three days. The upper extremities were most often involved and at times the edema was so extensive as to produce a continuous brawny swelling from the mid-arm to the tips of the fingers. On one occasion after a slight trauma to the forehead the lids of both eyes became enormously swollen and the patient could not see. The swelling spread to the cheeks and upper lip and the facial expression was so distorted that she could not be recognized. In three days the condition returned to normal.

Blood studies carried out during an attack of severe edema showed the following: hemoglobin 87 per cent, red blood cells 4,340,000, white blood cells 8,700; band forms 8 per cent, segmented 59 per cent, eosinophiles 2 per cent, lymphocytes 28 per cent and monocytes 3 per cent. Total serum protein 6.98 mg. per 100 c.c., albumin 5.22, globulin 1.76; albumin-globulin ratio 2.96. Blood sugar 98.0, sodium chloride 458, cholesterol 164, cholesterol ester 83.0, calcium 10.3 and phosphorus 4.0 mg. per cent. The heterophile antibody reaction showed agglutination in normal dilutions.

Further studies of the serum protein made during and after attacks are recorded in table 1. These findings seem to show an increased albumin-globulin ratio in the attack. The test for urine concentration was normal and the Van Slyke index was 70 per cent maximum clearance. This patient refused to return to the clinic for further study and treatment and so far as we know her condition is unchanged.

TABLE I  
Blood Serum Proteins\*

Date	Condition	Total Serum Protein	Albumin	Globulin	A-G Ratio
3/27/36	In attack	6.98	5.22	1.76	2.96
3/30/36	End of attack	7.25	4.98	2.27	2.2
4/3/36	Free interval	6.91	4.54	2.37	1.9
5/4/36	Free interval	6.98	4.2	2.78	1.51
5/22/36	In attack	6.82	4.72	2.10	2.25
5/25/36	Attack subsided	6.98	4.41	2.57	1.72
6/1/36	Attack	6.71	4.81	1.9	2.53
2/17/37	End of severe attack	7.66	4.95	2.71	1.83
4/12/37	In attack	7.02	4.85	2.17	2.23

\* All determinations were made from blood taken in the morning on an empty stomach.

It may be mentioned here that few of the reported deaths include autopsy findings. Griffith<sup>19</sup> treated a 34-year-old woman who died suddenly of laryngeal obstruction and necropsy revealed marked edema, tenseness and pallor of the larynx with only a small aperture present. Microscopic sections showed not only edema of the mucous membrane but also involvement of the submucosa, deeper connective tissue and muscles. Wason's report<sup>20</sup> of a 14-month-old child pronounced dead on arrival at the hospital, revealed marked edema of the pharynx and larynx with involvement of the lower respiratory tract. The microscopic picture of the pharynx was essentially one of edema involving all layers. The blood vessels and lymphatics were moderately dilated. The findings of Morris<sup>21</sup> were quite similar to the above. Obviously the edema in such cases must be extensive and deep to cause asphyxial death.

#### EMERGENCY TREATMENT

Since little progress has been made in the prevention of this type of edema it is important to stress the immediate treatment to be employed when the glottis

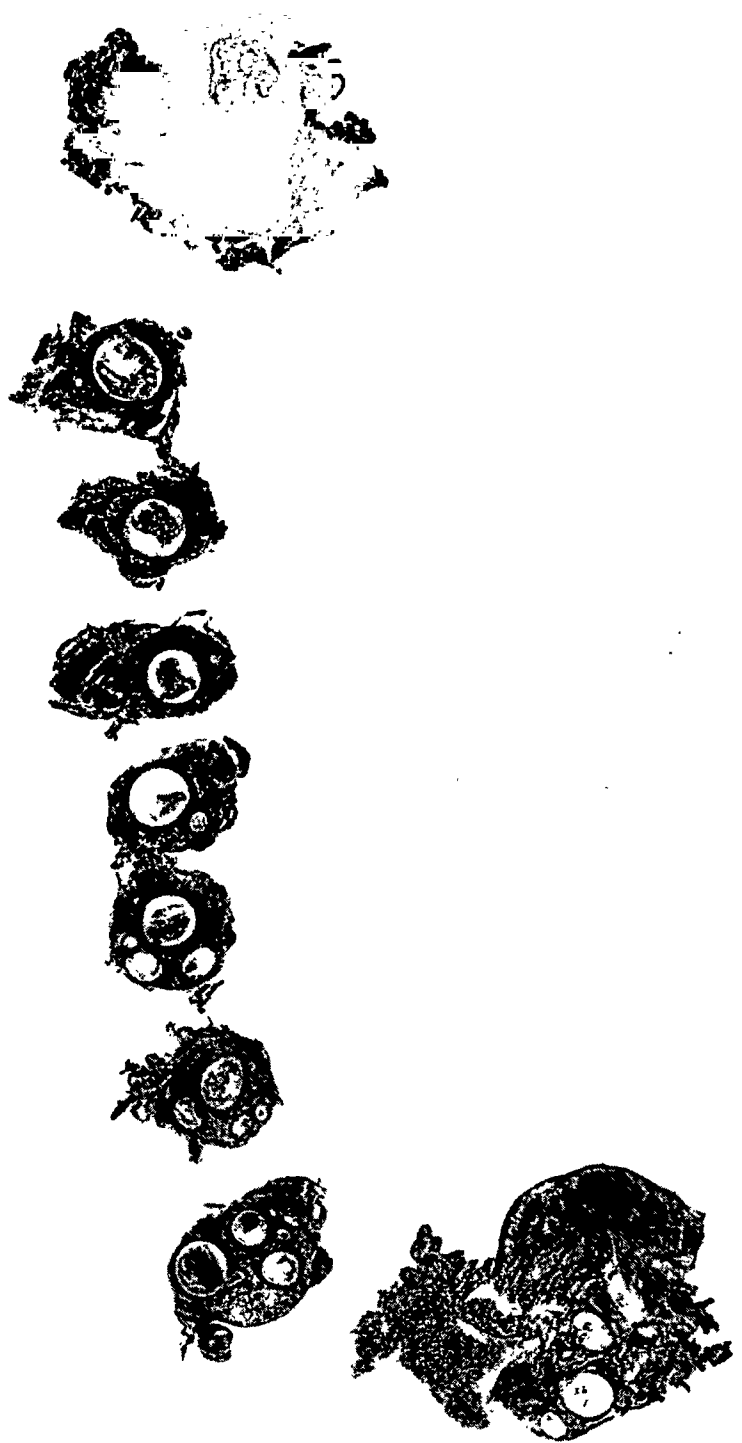


FIG. 1. Thrombosis of entire right main ovarian vein shown in serial cross sections from hilum of ovary to the inferior vena cava. Note thrombus projecting into the inferior vena cava.

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## TREATMENT OF UNDULANT FEVER WITH SULPHANIL-AMIDE; CASE REPORT\*

By AUSTIN B. CHINN, M.D., *Washington, D. C.*

THE use of sulphanilamide in the treatment of undulant fever has been recently advocated.<sup>1, 2, 3, 4</sup> In the case herein described, features other than the disappearance of fever seem to make it worthy of recording.

### CASE REPORT

C. R., a white male, aged 32 years, a department store executive, was first seen on May 14, 1938. He complained of chilly sensations, fever, sweats, and malaise. His

\* Received for publication August 18, 1939.



and the two layers of pericardium were fused and measured from 0.5 to 1.5 cm. in thickness. Microscopic sections of the fused portions revealed a dense mass of granulation tissue which was moderately well vascularized and showed focal infiltration of lymphocytes. Sections of the organizing fibrinopurulent exudate showed the formation of thick layers of young granulation tissue composed of actively proliferating fibroblasts and newly formed capillaries.

In situ, the heart appeared small. Its estimated weight was 275 grams. The myocardium of both ventricles was yellowish-brown and flabby. However, microscopically there were no areas of abscess formation or leukocytic infiltration. Sudan III stains revealed severe fatty degeneration of the muscle fibers. There were no mural thrombi within the atria. The valves showed no significant abnormality and the coronary arterial tree was not remarkable.

The lungs showed considerable hyperemia and edema, especially of the lower lobes. There were no foci of consolidation or abscess formation. The bronchial tree presented a moderately hyperemic, grayish-red mucosa and the lumina of the larger passages contained a slight amount of frothy, grayish-pink exudate.

The final pathologic diagnoses were: acute fibrinopurulent pericarditis with extensive organization; chronic constrictive pericarditis; thrombophlebitis of the uterine and ovarian plexuses of veins in the broad ligaments; thrombosis of the entire right main ovarian vein; subacute purulent endometritis; fatty degeneration of the myocardium; marked chronic passive hyperemia of the liver and spleen; pulmonary edema; hydrothorax (right 850 c.c.; left 250 c.c.); ascites (0.5 liter); subacute cystitis.

*Bacteriology:* Pure cultures of *Staphylococcus aureus hemolyticus* were recovered from the thrombi in the ovarian veins and from the pericardial exudate.

#### COMMENT

The sequence of events in this case is made plainly evident by the autopsy. Following an abortion, the patient developed a purulent endometritis. The inflammation extended into blood vessels in the wall of the uterus and led to an extensive thrombophlebitis of the pelvic veins. This evidently served as a source of invasion of the blood stream by septic emboli or bacteria which lodged in the pericardium, producing a suppurative inflammation. At autopsy no other site of embolic localization was found. The same organism, *Staphylococcus aureus hemolyticus*, was cultured from the pericardial exudate and from the thrombi in the ovarian veins.

When the patient was first studied clinically, she was in circulatory failure. The presence of distended peripheral veins and of an enlarged tender liver with ascites, together with suppression of the heart sounds and a paradoxical pulse led to a diagnosis of constrictive pericarditis. This lesion appeared to be related etiologically to the patient's abortion which occurred nine weeks previously, but the manner of association was not entirely clear. The autopsy revealed an extensive organizing fibrinopurulent pericarditis with partial obliteration of the pericardial sac and fusion of the visceral and parietal pericardium into one thick dense fibrous layer. This rigid tissue was responsible for the constriction which led to failure of the heart. The severity of the cardiac embarrassment was indicated anatomically by the marked pulmonary edema and hydrothorax, as well as by the passive hyperemia of the liver with central necrosis of the lobules and also ascites.

Suppurative pericarditis usually results from extension of infection in the lungs or mediastinum to the pericardium, either directly or by way of lymphatic vessels. It also occurs as a blood-borne infection, in association with a gener-

over, was in direct proportion to the concentration of antigen used, the inflammation at the site of the injected undiluted material being 4.5 cm. in diameter. Agglutination of the blood serum on this day against *Brucella abortus*, showed a positive test in a dilution of 1-640. On the fifth day of chemotherapy, the patient's temperature for the first time in three weeks dropped to normal in the morning, with an evening rise to 99.8° F. During the next two days it reached successively lower levels in the evening, and on the eighth day after starting the drug, it remained normal for 24 hours. From that time on he had no further fever. The skin reactions were maximum in intensity six days after starting the drug, and then faded gradually over a period of two to three weeks.

#### COMMENT

Two features of this man's illness seem worthy of mention. As a first consideration we have the appearance of positive intradermal reactions to *Brucella abortus* antigen following the administration of sulphanilamide to a patient with suspected undulant fever. This seems particularly significant since the three intracutaneous tests were interpreted as negative for six, eight and ten days, respectively, after injection, and became positive only after the patient had received maximum doses of sulphanilamide for four days. Moreover, appearing concomitantly with the positive skin tests, were serological agglutinins sufficient to give a positive test in a dilution of 1-640. The question naturally arises as to whether the antigen previously injected intradermally could not have given the positive agglutination. This seems unlikely, considering the height of the titer and the fact that previous agglutination tests, done following two of the intradermal injections, were negative. Welch, Wentworth, and Mickle<sup>5</sup> have recently reported upon determinations of the opsonocytophagic indices of persons with brucellosis before and after giving them sulphanilamide. They found phagocytosis to be increased after use of the drug and concluded that its administration may be of diagnostic aid in this disease. In three of the five cases they describe, moreover, agglutination tests which were negative before administration of the drug became positive after its use. It does not seem hypothetically impossible, therefore, that through the action of the drug, sufficient numbers of immune bodies may be produced to give a positive skin reaction and positive agglutination tests.

As a second consideration, we have the clinical recovery of a patient with apparent undulant fever, following the administration of sulphanilamide. The necessity for maximum dosage of the drug for successful treatment of the disease, as illustrated in this patient, is consistent with the experience of others. It is interesting that an earlier course of the drug in smaller doses and over a shorter period was without effect.

#### SUMMARY

1. In a patient with suspected undulant fever, three *Brucella abortus* intradermal tests, which had been negative for six, eight and ten days respectively, showed a positive reaction after the administration of large amounts of sulphanilamide. Appearing together with the positive skin tests were positive agglutination tests, though they, too, had been negative before giving the drug.

2. A case of undulant fever showed clinical recovery, following the administration of large doses of sulphanilamide.

## EDITORIAL

### *THE ABSORPTION AND EXCRETION OF IRON*

ALTHOUGH iron is an element vitally essential to all vertebrates, relatively little has been known regarding its exchange in the body. Iron unquestionably must be absorbed from the gastrointestinal tract, and there is good reason to believe that this occurs largely in the upper part of the small intestine. The details of its excretion are much less clear. Iron is normally present in the urine in only minute insignificant traces, and by exclusion it has been assumed that excretion occurs through the intestine. Some histological evidence has been advanced to support this view, but it is impossible to determine in this way whether iron which may be seen in the intestinal mucosa is being excreted or absorbed. It is also impossible to determine directly what portion of the iron in the feces may have been excreted and what has merely escaped absorption.

The total amount of iron in the body is small—normally only a little over four grams. Of this a large part, about 2.65 grams, is contained in the hemoglobin of the red cells. A small amount, about 0.3 gram, is present and functioning in other compounds in the tissues. Part is found in the myoglobin of the muscles, and part is known to be a constituent of certain oxidative enzymes present in all living cells. This iron is evidently essential to the life of the cells, as it never is abstracted for hemoglobin formation, even in the most severe anemias. In addition a larger and more variable amount, estimated at one-third to one-half of that in the hemoglobin, is stored in the tissues, chiefly in the spleen, liver and bone marrow, and is available for hemoglobin formation in case of need.

There is also a minute amount of non-hemoglobin iron in the plasma, from 60 to 150 micrograms per 100 c.c. This may be highly significant, nevertheless, since it is probably the form in which iron is transported in the body. This plasma iron is diminished in hypochromic anemias, but is increased in pernicious anemia.<sup>1</sup> In patients or animals with hypochromic anemia it rises after the administration of absorbable iron preparations, and its rise is, within limits, proportional to the size of the dose. In untreated pernicious anemia, on the other hand, no such rise occurs.<sup>2</sup>

It is probable that the average life of the red cells is about 30 days. Hence the cells from about 175 c.c. of blood will be destroyed and replaced daily. These contain about 25 grams of hemoglobin, and 85 milligrams of iron is therefore liberated. It has long been known that the great bulk of this iron is retained in the body and is either stored or immediately used

<sup>1</sup> HEMMELER, G.: *Serumeisen und Eisentherapie*, Schweiz. med. Wchnschr., 1939, lxix, 316.

<sup>2</sup> MOORE, C. V., et al.: *Studies in iron transportation and metabolism: IV. Observations on the absorption of iron from the gastrointestinal tract*, Jr. Clin. Invest., 1939, xviii, 553-580.

seriously ill she was cheerful and coöperative. The skin was cool and clammy and there was cyanosis of the face and mucous membranes. The neck veins were engorged and prominent. The lower extremities showed considerable edema which extended to the level of the sacrum.

The heart was questionably enlarged to the right, and there was marked suppression of the cardiac sounds. The pulse was rapid and regular but had a very small volume, at times was almost imperceptible, and was distinctly paradoxical. The bases of both lungs were dull to flat on percussion and showed diminished breath sounds and fremitus.

The abdomen was markedly distended and revealed shifting dullness as well as a distinct fluid wave. The liver was easily palpable and its right lower margin extended to the level of the umbilicus. The spleen was not palpable.

*Laboratory Findings:* The urine showed an average of 28 white blood cells per high power field. The red blood cell count was 3,100,000 with 60 per cent hemoglobin; the white blood cell count was 12,100 with 90 per cent polymorphonuclears. The Kline exclusion test was negative. The blood urea nitrogen was 6.5 mg. per 100 cubic centimeters and the blood sugar was 69 mg. per 100 cubic centimeters.

Roentgenologic examination of the chest revealed massive bilateral pleural effusion. An electrocardiographic tracing showed very low amplitude of the T-waves in the standard leads and a diphasic T-wave in Lead IV. These findings suggested myocardial damage.

*Hospital Course:* The patient was practically moribund on admission. She presented the picture of circulatory failure and cardiac compression, and the diagnosis of constrictive pericarditis was suggested. However, the etiology of this lesion was not clear.

Thoracentesis, performed on the evening of admission, removed 1 liter of clear yellow fluid from the right pleural cavity with considerable relief to the patient. The next morning her condition was about the same. A liter of clear fluid was removed from the left pleura. In the next few hours her cyanosis deepened and she became hard to arouse. Moist râles were heard throughout both lungs. The respirations became very shallow and the pulse was virtually imperceptible. Death occurred 26 hours after admission.

*Postmortem Examination:* Autopsy was performed 8 hours after death. Externally the body showed nothing unusual, except for a light brown, frothy discharge from the mouth. The skin was smooth and elastic and showed no petechiae or icterus.

The peritoneal cavity contained approximately 500 c.c. of clear, yellow, serous fluid, of specific gravity 1.005. The surfaces of the peritoneum were grayish-pink and hyperemic and showed no exudate. No fibrous adhesions were found in the pelvis.

Both leaves of the broad ligament were thickened and indurated, due to extensive thromboses of the uterine and ovarian plexuses of veins. Firm cords of thrombotic veins extended from the cornua of the uterus to the ovaries. The vessels varied from several millimeters to 1 cm. in diameter and their lumina contained impacted, friable, mottled grayish-red and white thrombi. Microscopic sections showed that these thrombi were composed of irregular or laminated strands of fibrin, masses of partly preserved erythrocytes and necrotic polymorphonuclear cells. In some veins there was slight organization of the thrombus at the site of intimal attachment. The vessel walls were well preserved although the adventitial and periadventitial connective tissue showed focal areas of lymphocytic infiltration.

The right main ovarian veins were completely occluded by thrombosis and formed a thick cord-like structure, extending up into the abdomen from the ovary. They terminated in a single large vein, 1.5 cm. in diameter, from whose distal end a thrombus projected into the lumen of the inferior vena cava (figure 1). The left main ovarian veins, the hypogastric veins and the uterine arteries contained no thrombi.

considerable evidence that this is actually the case. In earlier experiments on anemic depleted dogs which had been maintained on a diet low in iron Whipple found that if food rich in iron, or ordinary iron salts in moderate doses were administered, a large part was absorbed and retained. Under favorable conditions, and with small doses (40 mg.), from 30 to 45 per cent of the iron was retained. This was followed within three to four days by a sharp increase in circulating hemoglobin. This increase, they believe, accurately measures the total amount of iron absorbed, since iron injected parenterally in such animals was totally utilized in forming new hemoglobin. In the normal dog, extra iron administered by mouth was not retained.

These conclusions have been confirmed by a duplication of these studies using radio-active iron compounds.<sup>6, 7</sup> When administered to anemic dogs substantial amounts were absorbed and retained. Within two to four hours after a single dose radio-active iron appeared in the plasma. It reached a maximum level after about six hours and then dropped off markedly, indicating that absorption is practically completed within 18 hours. The shape of this curve confirms the view that absorption occurs in the small intestine. Traces of radio-active iron were demonstrable in the red cells after four hours in some cases. After 24 hours substantial amounts were found, and substantially all the iron absorbed was incorporated in hemoglobin within four to seven days; and even within two to three days if hemoglobin production was active when the dose was given. The percentage of the administered iron which was absorbed varied considerably, and, in general, varied inversely with the size of the dose given. It was never complete, but ranged from 47 per cent of a 5 mg. dose to 3.2 per cent when 115 mg. were given.

When radio-active iron was administered to plethoric dogs only insignificant traces were absorbed—about 0.05 per cent.

Several observers,<sup>8</sup> however, have reported that when, in balance studies, very large doses of iron were administered to patients, or to normal individuals, considerably more iron was absorbed than could be accounted for by the hemoglobin formed. Presumably this is added to the body reserve stores. How far this plethora of iron can be pushed is not yet known.

It seems clear from these studies that there is no mechanism for controlling the excretion of iron, or even for effectively bringing it about under ordinary conditions, although in certain pathological states substantial amounts may be excreted in the bile. There is merely a wastage of small and relatively constant amounts of iron into the feces, probably not over

<sup>6</sup> HAHN, P. F., et al.: Radioactive iron and its metabolism in anemia. Its absorption, transportation and utilization, Jr. Exper. Med., 1939, lxix, 739-753.

<sup>7</sup> HAHN, P. F., et al.: The utilization of iron and the rapidity of hemoglobin formation in anemia due to blood loss, Jr. Exper. Med., 1940, lxxi, 731-736.

<sup>8</sup> FOWLER, W. M., and BARER, A. P.: The treatment of iron deficiency anemias, Jr. Am. Med. Assoc., 1939, cxii, 110.

The uterus was of normal size but was markedly retroverted. Several small thrombotic veins were found in the outer portion of myometrium of the fundus and body. The endometrial surface was dark red and smooth, except for a small portion of the fundus anteriorly which was covered by a thin, yellow, granular exudate. Microscopically this area showed a necrotic fibrinopurulent endometritis. No placental or decidual tissue was found. The Fallopian tubes and ovaries showed no significant gross or microscopic change. No corpus luteum was found.

The liver weighed 1450 grams and was the seat of severe passive hyperemia of nutmeg type. There were no areas of abscess formation and the portal veins were free of thrombi. Microscopically there was diffuse hyperemia of the intralobular sinusoidal network with severe compression necrosis of liver cells in the central zones, in the periphery of which there was a considerable polymorphonuclear cell infiltration. In the outer portions of the lobules the cells were loaded with small globules of fat. Special stains showed neither iron-bearing pigment nor any increase in connective tissue.

The spleen weighed 75 grams and was not noteworthy.

The entire gastrointestinal tract, the adrenals, the kidneys and the brain showed no significant gross or microscopic change. There was a mild subacute cystitis.

The thoracic organs occupied their usual positions. The right and left pleural cavities respectively contained approximately 850 c.c. and 250 c.c. of clear, yellow, serous fluid of specific gravity 1.008. There were extensive fibrous adhesions binding the pericardium to the mediastinal surfaces of the pleura.

The visceral and parietal layers of pericardium were markedly thickened and fibrous, and enclosed an organizing fibrinopurulent exudate (figure 2). There were

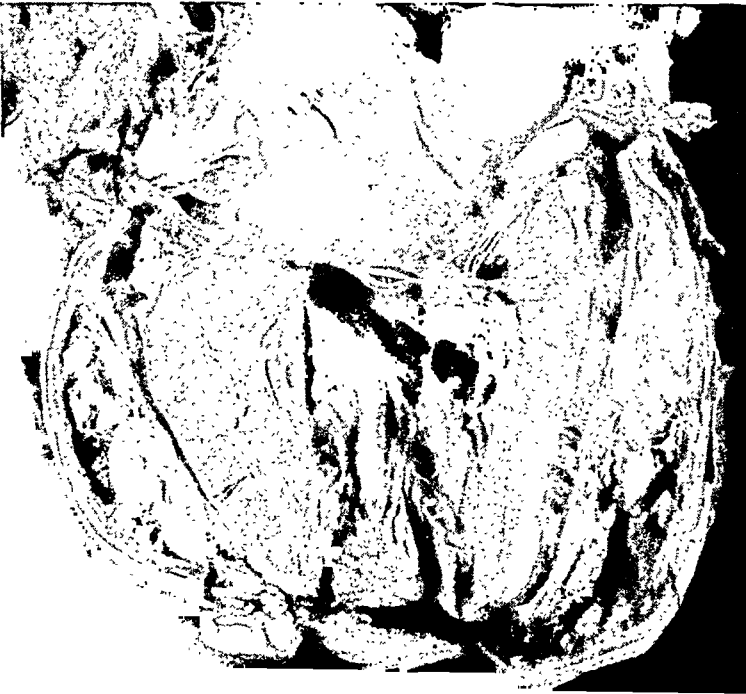


FIG. 2. Cicatrized fibrinopurulent pericarditis.

approximately 120 c.c. of yellowish-brown, purulent fluid, as well as pale yellow inspissated masses of fibrin in the pericardial sac. In some places, especially at the base of the heart and about the atria, the exudate was both organized and cicatrized

## REVIEWS

*The Building of a Nation's Health.* By SIR GEORGE NEWMAN, G.B.E., K.C.B., M.D., F.R.C.P. 479 pages; 15 × 23 cm. MacMillan and Co., Limited, London, New York. 1939. Price, \$6.00.

In the Second Annual Sedgwick Memorial Lecture in 1924 Dr. William Henry Welch referred to the great sanitary awakening, preceding the modern public health era, which began with the creation of the General Board of Health in England in 1848, and he said in part: ". . . every student of public health should read again and again the complete story as told so fascinatingly and authoritatively by Sir John Simon in his *English Sanitary Institutions*." The student can now welcome a worthy continuation of this story that closed with the second edition of *English Sanitary Institutions* in 1897. Sir George Newman in *The Building of a Nation's Health* first sketches the backgrounds of the public health movement as presented by Sir John Simon and then describes the modern trends and achievements in official public health organizations on a nation-wide scale in Great Britain. The author of the present volume served as the first Chief Medical Officer of the Ministry of Health from 1919, when the Ministry was created, until 1935 and his evaluations of the many different kinds of national and local health programs have their roots in years of first-hand, practical experience.

The first chapter includes the historical events preceding the first national movement in public health in England: (1) the appointment of William Farr in 1839 as the medical statistician to the Registrar General; (2) Sir Edwin Chadwick's synoptical volume in 1842 of his Poor Law Commission report, "Sanitary Condition of the Labouring Population of Great Britain"; and (3) the enactment of the Public Health Act of 1848 inaugurating the General Board of Health. Although the Board ceased to exist as early as 1858 by reason of expiration of legislative provisions, it had laid the foundation for Parliamentary action in the interests of health programs. By 1869 Mr. Gladstone had appointed a Royal Sanitary Commission whose recommendations were incorporated in the Public Health Acts, first of 1871, second of 1872 and third of 1875. The Act of 1871 created the Local Government Board which functioned until the birth of the Ministry of Health in 1919.

In Chapter II there is a detailed account of the governance of English medicine by the State, of which the major event was probably the Medical Act of 1858 creating a *Medical Register* of qualified practitioners and providing for the maintenance of this Register by a "*General Council* of Medical Education and Registration of the United Kingdom" directly responsible to the Privy Council. This *General Council* continues today and consists of representatives of the Crown, of the Universities and of the Licensing Corporations. It is of interest to the American reader to note that the Council has become an agent of *Education* as well as an office of *Registration*. The Council reviews medical curricula and makes recommendations and one of its valuable collateral activities in the graduate field has been the registration of Diplomas in Public Health, a statutory duty imposed upon it by the Medical Act of 1886. The author entitles the third Chapter "New Spirit in English Medical Education" and in it he emphasizes the influence of Sir William Osler in all branches of medical education. The Earl of Athlone was appointed Chairman of a Post-Graduate Medical Committee by the Minister of Health (Dr. Addison) in 1921 and the work of the Committee reached fruition in the formal opening of the new London School of Hygiene and Tropical Medicine on July 18, 1929.

Sir George Newman in Chapter IV recounts the events leading up to the establishment in 1919 of the Ministry of Health, the principal health subjects within its

alized pyemia or a septicemia. In the present case the suppurative pericarditis was an isolated lesion which evidently had its source in a postabortive pelvic thrombophlebitis and was carried by way of the blood stream to the pericardium. The pericardial inflammation was quickly organized and within a period of several weeks sufficient scar tissue was formed to produce cardiac compression. Had the symptoms of constrictive pericarditis developed at a later time, the etiologic relation of the disease to a previous pelvic infection might easily have been overlooked. It appears probable that at least some cases of chronic constrictive pericarditis of obscure etiology originate in a similar manner as a result of metastasis from a pyogenic infection elsewhere in the body.

In retrospect the surgical implications of this case are important. The suppurative pericarditis developed within several weeks after the patient's abortion and was followed by the development of constrictive pericarditis. The symptoms were due to effects upon the heart of exudate and scar tissue, and not to the infection itself. In fact the pericardial lesion was silent until the mechanical effects of inflow stasis became manifest. Had a diagnosis of constrictive pericarditis been made early in the disease, drainage of the pericardial sac, by pericardiotomy, and removal of pericardial scar tissue might have been feasible. In Dujol's case<sup>1</sup> of suppurative pericarditis following an infected abortion the pericardial sac was aspirated and 200 c.c. of purulent fluid were removed. This was believed to be an important factor in the patient's recovery.

#### SUMMARY

This report describes a case of suppurative pericarditis complicating a post-abortive thrombophlebitis of the pelvic veins in a 28 year old woman. Shortly after abortion the patient rapidly developed the symptoms of severe compression of the heart and died in circulatory failure within a period of eight weeks. An autopsy revealed extensive thromboses of the uterine and ovarian veins and an isolated suppurative pericarditis which showed considerable organization. The resulting thick pericardial scar tissue was responsible for the fatal constriction of the heart. The metastatic nature of the pericarditis was clearly established by the recovery of the same organism, *Staphylococcus aureus hemolyticus*, from the thrombi in the ovarian veins as from the pericardial exudate.

#### REFERENCE

1. DUJOL, G.: Péricardite purulente à staphylocoques au cours d'une infection post-abortum, Bull. Soc. d'obst. et de gynec., 1929, xviii, 247.



is realized that the author makes no attempt to cover the field of internal medicine in detail.

W. K. W.

*Immune-Blood Therapy of Tuberculosis.* By JOSEPH HOLLÓS, M.D. 197 pages; 22 × 14.5 cm. Bruce Humphries, Inc., Boston. 1940. Price, \$2.50.

*Immune-Blood Therapy of Tuberculosis*, by Dr. Joseph Hollós, takes up a mode of therapy which the author has been using for 30 years. To obtain immune-blood, rabbits are immunized with a culture of human and bovine tubercle bacilli. From the immunized animals blood is withdrawn from the vein, hemolized, freed from albumin, and diluted 1-100,000. This is the "original immune-blood."

This blood has a dual effect when injected or rubbed into the skin of hypersensitive tuberculous patients. In larger doses it produces many focal and constitutional symptoms through its lytic effect on tubercle bacilli in the patient, and in smaller doses relieves constitutional symptoms by its antitoxic effect.

Dr. Hollós' claims for this treatment are little short of miraculous and most of the volume consists of case reports personally followed by the author. The data are far too meagre to allow one to draw strictly objective conclusions. In the latter part of the book the author includes such diseases and symptoms as rheumatism, Graves' disease, dementia praecox, epilepsy, dysmenorrhea, leukorrhea, neurasthenia and various gastrointestinal symptoms as part of a picture of tuberculous intoxication in the absence of clinically active tuberculosis of the lung or other organs of the body. He does not hesitate to undertake the treatment of these conditions with "immune-blood therapy" and claims results equally as good as in the manifest tuberculous.

Dr. Hollós feels that the medical profession has been amiss in not accepting his therapy for tuberculosis but unfortunately the magnitude of the claims, the lack of control material and the lack of objectivity in presenting the subject make one hesitate before advocating any change in this point of view.

M. S. S.

*The Newer Knowledge of Nutrition.* By E. V. McCOLLUM, ELSA ORENT-KEILES and HARRY G. DAY. Fifth Edition. 701 pages; 15 × 22 cm. Macmillan Co., New York. 1939. Price, \$4.50.

The fifth edition follows the fourth by ten years. It is a nutritionist's *vade mecum* and no stranger to the majority of internists. It preserves the chronological approach, beginning with the history of nutrition, and progressing through bodily requirements to the modern concept of dietary essentials. A chapter each is given to carbohydrates, fats, and proteins. Much of McCollum's own work is included in the discussion of minerals in the diet. Vitamins are thoroughly dissected, and here the reader can find all those usually referred to as: "and many other factors," tracked down and specified in their proper relationship to the vitamin family alphabet.

Pica in animals is discussed along with the dietary habits of different ages and different parts of the world. Faddists are appropriately and rationally spanked. The effect of racial factors and modern transportation is elaborated upon. Diet in relation to teeth and caries is thoroughly considered, and a summary on the prevention of tooth decay is particularly interesting.

Throughout the book the perspective is broad, the judgments reasoned, and the conclusions logically based on facts previously mentioned. Several interesting tables are included concerning vitamins, and there are good bibliographic references at the end of each chapter.

C. A.

for synthesis of new hemoglobin. It has been supposed that a significant amount is lost by excretion and has to be replaced from the food.

The need for iron varies with age and sex. It is greatest during the period of growth, both in young children and in adolescents; and in women who are menstruating as well as during pregnancy and lactation. Except in the presence of hemorrhage or active disease, it is only under these conditions that hypochromic anemia commonly develops. In normal adult males, in the absence of bleeding, the need is less. Recent balance studies show that this need is extremely small. Lintzel<sup>3</sup> maintained iron balance on an intake of only 1 mg. a day.

The experiments of McCance and Widdowson<sup>4</sup> cast doubt even on the possibility of the excretion of iron in significant amounts. They studied six normal individuals; first, during a control period in which they were in iron balance on an ordinary diet containing 7 mg. of iron daily. In a second period during which an additional 6 mg. of iron was given daily, by mouth, there was a corresponding increase in the iron in the feces; balance was maintained. During a third period, the extra iron, 7 mg. a day, was given by vein. Except for a slight but definite increase in the iron excreted in the urine during the first 20 minutes following the injection, this entire amount was retained. Since these individuals had been in iron balance and undoubtedly had adequate reserve stores of the metal, a substantial amount of this surplus iron should have been excreted if excretion plays any significant rôle in controlling iron metabolism.

More direct evidence as to this point has been furnished by the experiments of Whipple and his colleagues on dogs which have been depleted of iron and rendered anemic by repeated bleeding. By using iron salts containing radio-active iron, they were able to trace its distribution in the body tissues and excreta.<sup>5</sup> After injecting 100 to 250 mg. of radio-active iron as ferrous gluconate intravenously into dogs, whether anemic or plethoric, they found only very small amounts of this iron in the feces. During the first three to 15 days after the injection, appreciable amounts were found, in all from 2 per cent to 8 per cent of the injected iron. The daily excretion then fell to 50 to 400 micrograms, and this was maintained over an indefinite period. No more was excreted by the plethoric dog than by the anemic dog. They likewise conclude from these experiments that the dog excretes iron with difficulty, and that excretion can not play an important rôle in controlling iron metabolism.

Since, except in the disease hemochromatosis, iron is not stored in the tissues in unlimited quantities, some method of control must be exercised, and by exclusion this must be by varying the rate of absorption. There is

<sup>3</sup> LINTZEL, W.: Zur Frage des Eisenstoffwechsels. V. Ueber den Eisenbedarf des Menschen, *Ztschr. f. Biol.*, 1929, lxxxix, 342.

<sup>4</sup> McCANCE, R. A., and WIDDOWSON, E. M.: The absorption and excretion of iron following oral and intravenous administration, *Jr. Physiol.*, 1938, xliv, 148-154.

<sup>5</sup> HAHN, P. F., et al.: Radioactive iron and its excretion in urine, bile and feces, *Jr. Exper. Med.*, 1939, lxx, 443-451.

Course No. 3. Advanced General Medicine—Harvard University Medical School  
(3 weeks—March 31 to April 19, 1941)

*Boston, Mass.*

Dr. Paul D. White, Director

Course No. 4. Cardiology—Harvard University Medical School  
(1 week—April 14 to 19, 1941)

*Boston, Mass.*

Dr. Chester S. Keefer, Director

Course No. 5. Gastro-enterology—Boston University School of Medicine  
(1 week—April 7 to 12, 1941)

*Ann Arbor, Mich.*

Dr. Cyrus C. Sturgis, Director

Course No. 6. General Medicine—University of Michigan Medical School and  
University Hospital  
(2 weeks—April 7 to 19, 1941)

*New York, N. Y.*

Dr. Robert A. Cooke, Director

Course No. 7. Allergy—The Roosevelt Hospital, Department of Allergy  
(2 weeks—Dates yet to be determined)

*Columbus, Ohio*

Dr. Charles A. Doan, Director

Course No. 8. Hematologic Dyscrasias—Ohio State University College of Medicine  
(1 week—April 14 to 19, 1941)

*Philadelphia, Pa.*

Dr. William D. Stroud, Director

Course No. 9. Cardiology—University of Pennsylvania Graduate School of Medicine  
(2 weeks—April 7 to 19, 1941)

The two courses in Allergy have been correlated and essentially will cover the same subject matter. The course in General Medicine at the University of Michigan Medical School and the course in Hematology at the Ohio State University College of Medicine will be a repetition of the same courses given under the auspices of the College in the spring of 1940. The advanced course in General Medicine under the direction of Dr. James H. Means of Harvard University Medical School has been organized as a super-advanced course, covering a period of three weeks.

A one week's course in Cardiology and a one week's course in Gastro-enterology have been scheduled in Boston on alternate weeks, giving members who desire an opportunity to take both courses.

Detailed bulletins of the courses will be distributed to all members of the College as soon as ready.

1 mg. a day, which may be derived in part at least from desquamated epithelial cells.

On the other hand the amount of iron absorbed is adjusted, within limits, to the need of the body for iron. The mechanism by which control of this is brought about has not been demonstrated. It seems probable, however, as McCance and Widdowson suggested, that an important factor is the relative concentration of diffusible iron in the intestinal contents, and in the plasma and intestinal epithelium. In iron deficiency states in which the plasma iron is low, iron is readily absorbed. If the body is adequately supplied, the plasma iron is higher, and iron is not absorbed unless its concentration in the intestinal contents is raised to an unnaturally high level by giving large doses of medicinal iron. What part, if any, specific activities of the epithelial cells may play is not known. Precise knowledge of this mechanism must await further investigation.

P. W. C.

Chairmen are as follows:

- Dr. Reginald Fitz—Committee on Clinics
- Dr. Soma Weiss—Committee on Panel Discussions
- Dr. F. Gorham Brigham—Committee on Entertainment
- Dr. Howard B. Sprague—Committee on Auditorium
- Dr. Earle M. Chapman—Committee on Transportation
- Dr. Dwight O'Hara—Committee on Publicity

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#### NORTH CAROLINA MEMBERS HOLD 1940 REGIONAL MEETING

Fellows and Associates of the American College of Physicians of North Carolina held their Sixth Annual Regional Meeting at Chapel Hill, October 11–12, 1940, under the Governorship of Dr. Charles Hartwell Cocke. While this was the sixth annual get-together, it was only the second meeting in which the group had a scientific program. Dr. Paul F. Whitaker, F.A.C.P., Kinston, was Chairman of the Program Committee, and the scientific program was declared a most excellent one. Over 50 physicians out of a total of 82 Fellows and Associates in the State of North Carolina were in attendance. The scientific program occurred on Friday afternoon, October 11, and Saturday morning, October 12. On Friday evening a dinner was held at the Carolina Inn. Governor Cocke acted as Toastmaster and Dr. James D. Bruce, President of the College, delivered an address on "Recent Trends in Postgraduate Medical Education."

*Friday Afternoon, October 11, 1940, 2:30 o'clock*

(Auditorium, Medical Building)

#### *Symposium on Cholecystic Disease*

1. Etiology and Pathology of Cholecystic Disease. DR. EDWARD J. WANNAMAKER, Charlotte, N. C.
2. Symptoms and Signs. DR. SIDNEY F. LEBAUER, Greensboro, N. C.
3. Roentgenologic Consideration. DR. W. T. RAINEY, Fayetteville, N. C.
4. Laboratory Consideration. DR. E. B. CRAVEN, JR., Lexington, N. C.
5. Diagnosis (Correlation of History, Physical Examination, Laboratory and X-Ray Evidence). DR. WINGATE M. JOHNSON, Winston-Salem, N. C.
6. Differential Diagnosis. DR. WALTER R. JOHNSON, Asheville, N. C.
7. Management. DR. JULIAN M. RUFFIN, Durham, N. C.

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*Saturday Morning, October 12, 1940, 9:00 o'clock*

1. A Report of an Unusual Case of Leukemia. DR. K. P. TURRENTINE, Kinston, N. C.
2. The Psychoneuroses. DR. FREDERICK R. TAYLOR, High Point, N. C.
3. Fatigue. DR. JAMES D. BRUCE, Ann Arbor, Mich.
4. Recent Advances in Diseases of the Chest. DR. S. M. BITTINGER, Black Mountain, N. C.
5. Phytobezoars with Case Report. DR. JAMES H. McNEIL, North Wilkesboro, N. C.

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#### REGIONAL MEETING—ILLINOIS AND WISCONSIN MEMBERS

The Sixth Annual Regional Meeting of Illinois members (outside of Cook County) of the College was held at Rockford, Ill., Wednesday, October 16, 1940. Joined with the Illinois members were members of the College from Wisconsin. Dr. Samuel E. Munson, Governor for Southern Illinois, Springfield, and Dr. Elmer L.

jurisdiction and its statutory functions among which medical research and coöperation with the medical profession occupy important places. The author in Chapter V attributes the final awakening of local authorities in public health in England to the success of the governance and medical leadership of the Ministry of Health, and in support of this he cites abounding documentary evidence. In Chapters VI, VII, VIII, IX, X, and XI the latest functions of national and local official health agencies pass in review before the reader—procedures in the fields of school medical service, including the rôles of the special school, physical education and recreation, maternity and infant hygiene, the nutrition of the people, and the welfare of the industrial worker.

In his Chapter (XII) "Health Insurance and Medical Research" and the succeeding one (XIII) "Whence and Whither," Sir George Newman details many telling arguments in favor of the leadership of the State in medical care as it exists in England. He declares the value of public health education in national and local programs is indisputable and states (p. 448): "No credit to preventive medicine stands higher in England than its service in the dissemination of knowledge on the control of disease, on the way of freedom from its thralldom, and on the more abundant life which full health of body and mind can bring to us all." The final chapter (XIV) is a glowing tribute to Sir Robert Laurie Morant, a devoted Civil Servant who contributed throughout his life to the advancement both of State education and public health. He succeeded in bringing the National Insurance Act within the scope of the Ministry of Health, the foundations of which he laid as its first Permanent Secretary during the 18 months before his death in 1920.

*The Building of a Nation's Health* is a splendid compendium of recent public health philosophy based primarily upon English experiences of the past, particularly since the turn of the century. Sir George Newman clearly traces the historical development of each health topic considered and the book, delightfully readable as it is, becomes a valuable reference volume for the student in public health who wishes a brief and authoritative account of the steps leading to our present attitudes and doctrines in public health administration. The frequent marginal, topical annotations in the book are convenient and helpful, and the chapter introductory quotations are especially well-chosen. The book contains five excellently produced portrait photographs and one of these entitled "Sir William Osler in His Library" is unusual. The format of the publication is pleasing.

W. H. F. W.

*Fundamentals of Internal Medicine.* By WALLACE MASON YATER, A.B., M.D., M.S., F.A.C.P. 1021 pages; 25 × 17 cm. D. Appleton-Century Company. 1940. Price, \$9.00.

This book takes its place in the medical library between a compend and a detailed textbook on the subject. The author has accomplished his aim of presenting the minimal amount of knowledge of clinical medicine a medical student or general practitioner should have at his fingertips.

Dr. Yater presents his material in a clear-cut, easily readable manner. Each section starts with an outline of the subjects to be discussed, followed by a brief introduction which takes into consideration physiology, important laboratory examinations, and symptoms distinctive of the system under discussion. The book is profusely illustrated, and the important points under each disease are set out in bold type. The sections are concluded with recommended texts for further reading.

The book seems a little out of balance in parts, as less space is devoted to discussion of diseases of the kidneys than to diseases of the eye and ear, two subjects rarely covered in a textbook of internal medicine.

The reviewer is favorably impressed with this book, and undoubtedly students of medicine and general practitioners will find much useful information provided it

Dr. Alfred B. Olsen, F.A.C.P., has accepted the position of psychiatrist to the Wabash Valley Sanitarium, LaFayette, Ind.

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Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "The Health of the Football Official" before the Eastern Intercollegiate Football Association, at Hershey, Pa., September 7, 1940.

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The 13th Annual Spring Clinical Conference of the Dallas Southern Clinical Society will be held March 17-20, 1941, in Dallas, Tex. Dr. Everett C. Fox, F.A.C.P., is president of this Society and Dr. W. Grady Reddick, F.A.C.P., is chairman of the Executive Committee. Among the guest speakers who will present papers at this meeting are Dr. Clifford J. Barborka, F.A.C.P., Chicago, Ill., Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, Pa., and Dr. Soma Weiss, F.A.C.P., Boston, Mass.

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The Omaha Mid-West Clinical Society held its 8th annual assembly, October 28 to November 1, 1940. Among the guest speakers at the General Assemblies of this meeting were the following:

Dr. John Thomas Murphy, F.A.C.P., Toledo, Ohio—"X-Ray Treatment in Cancer of the Skin," "Cancer of the Cervix," and "Taking the 'X' Out of X-Ray Treatment";

Dr. Reginald Fitz, F.A.C.P., Boston, Mass.—"Nephritis and Nephrosis," "The Changing Picture of Diabetes Mellitus," and "The Management of Hypertension";

Dr. Samuel Ayers, Jr., F.A.C.P., Los Angeles, Calif.—"The Problem of Acne and Seborrhoeal Conditions" and "Pyogenic Dermatoses—Diagnosis and Treatment";

Dr. Horton Ryan Casparis, F.A.C.P., Nashville, Tenn.—"Gastro-Intestinal Allergy of Infants and Children" and "Behavior Problems in Children";

Dr. Wendell Stanley Muncie (Associate), Baltimore, Md.—"The General Practitioner's Stake in Psychiatric Therapy" and "Chronic Fatigue—Differential Diagnosis and Treatment";

Dr. George Herrmann, F.A.C.P., Galveston, Tex.—"The Clinical Study of Patients" and "Common Cardiac Emergencies and Their Management."

The following were among those who were Leaders of the Round Table Discussions:

Dr. Reginald Fitz, F.A.C.P., Boston, Mass.—"The Elderly Diabetic";

Dr. Horton Ryan Casparis, F.A.C.P., Nashville, Tenn.—"Causes of Convulsive Seizures in Childhood";

Dr. Wendell Stanley Muncie (Associate), Baltimore, Md.—"Childhood Behavior Problems";

Dr. George Herrmann, F.A.C.P., Galveston, Tex.—"Pulmonary or Coronary Thrombosis???—Treatment."

Dr. Frank H. Bethell, F.A.C.P., Ann Arbor, Mich., and Dr. Frank J. Heck, F.A.C.P., Rochester, Minn., were among those who presented a symposium on "The Anemias."

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Dr. Russell L. Cecil, F.A.C.P., New York, N. Y., recently addressed the Academy of Medicine of Cleveland, Ohio, on "Present Status of Serum Therapy and Chemotherapy in the Treatment of Pneumonia."

## COLLEGE NEWS NOTES

### POSTGRADUATE COURSES ARRANGED BY THE AMERICAN COLLEGE OF PHYSICIANS

Winter and Spring of 1941

The Advisory Committee on Postgraduate Courses and the Committee on Educational Policy of the American College of Physicians announce the following courses, arranged through the generous coöperation of the directors and the institutions at which the courses will be given.

This is the fourth year of this activity by the College. The courses are offered especially for Fellows and Associates of the College, but where facilities are available, they are open to those preparing either to meet the requirements for membership in the College or certification by the American Board of Internal Medicine.

The courses are made available by the College to its members at minimum cost, because the College itself has assumed full responsibility for promotion, advertising, printing and registration as its contribution. This schedule of courses is announced after a complete survey of the needs and wishes of the College members. Due to a growing demand for courses at other periods of the year than just preceding the Annual Session, the College has initiated this year two courses in February and plans to extend the schedule to other seasons of the year in succeeding years, if the demand for such courses justifies this extension. The number of courses to be given as pre-meeting courses, just preceding the Twenty-fifth Annual Session at Boston, April 21-25, has been extended and the type of courses has been selected according to the recommendations of the membership.

*Fees*—The registration fee, regardless of the institution or course selected, is based on \$20.00 for each week. One-half of the registration fee is payable at time of registration and the balance shall be paid not later than one week in advance of the opening of any course.

The College will record all registrations with the respective institutions offering courses and will directly reimburse those institutions for each student-physician at the specified fee. A matriculation card will be sent each registrant when his fee has been paid in full.

#### February Courses

*St. Louis, Mo.*

Dr. Harry L. Alexander, Director

Course No. 1. Allergy—Washington University School of Medicine  
(2 weeks—February 10 to 22, 1941)

*Rochester, Minn.*

Dr. Edgar V. Allen, Director

Course No. 2. Gastro-enterology—Mayo Foundation of the University of Minnesota  
(2 weeks—February 10 to 22, 1941)

#### Pre-Meeting Courses

*Boston, Mass.*

Dr. James H. Means, Director



Dr. Arthur C. DeGraff, F.A.C.P., New York, N. Y., addressed a meeting of the Academy of Medicine of Northern New Jersey in Newark, October 17, on "The Present Status of Digitalis Therapy."

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Dr. Jay Arthur Myers, F.A.C.P., Minneapolis, Minn., addressed a meeting of the Bergen County (N. J.) Medical Society on "Follow-up Work in Tuberculin Testing Surveys" at Bergen Pines, October 8, 1940.

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Dr. Russell L. Cecil, F.A.C.P., New York, N. Y., was recently made an honorary member of the Argentine League Against Rheumatism.

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Duke University School of Medicine and Duke Hospital, Durham, N. C., presented a symposium on diseases of metabolism and of the blood-forming organs, October 31 to November 2, 1940. Among the guest speakers were:

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.—"Hemorrhagic Diseases";

Dr. Claude E. Forkner, F.A.C.P., New York, N. Y.—"The Leukemias";

Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass.—"Diabetes and Its Treatment";

Dr. Eugene F. DuBois, F.A.C.P., New York, N. Y.—"Clinical Application and Interpretation of the Basal Metabolic Rate";

Dr. George R. Minot, F.A.C.P., Boston, Mass.—"Some Aspects of the Etiology, Diagnosis, and Treatment of Iron Deficiency Anemias and Pernicious Anemia";

Dr. Frank A. Evans, F.A.C.P., Pittsburgh, Pa.—"The Nature of Obesity, Its Prevention and Cure";

Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn.—"What Is Hyperinsulinism?"

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Dr. Tom Douglas Spies, F.A.C.P., Cincinnati, Ohio, presided at a symposium on vitamin deficiencies at the semi-annual meeting of the Ohio State Hospital Physicians' Association held in Cincinnati, October 3-4, 1940.

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Dr. Edgar V. Allen, F.A.C.P., College Governor for Minnesota, Rochester, addressed the Mahoning County (Ohio) Medical Society on "Peripheral Circulation" at their meeting in Youngstown, October 22, 1940.

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Dr. Ferdinand C. Helwig, F.A.C.P., Kansas City, Mo., recently addressed the Tulsa County (Okla.) Medical Society on "Clinical and Experimental Studies of Coronary Disease with Special Emphasis on Trauma," at Tulsa.

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Dr. Wann Langston, F.A.C.P., Oklahoma City, Okla., spoke on "Blood Dyscrasias" at a recent meeting of the Southern Oklahoma Medical Association in Shawnee.

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Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass., was one of the speakers at the 10th annual fall clinical conference of the Oklahoma City Clinical Society held in Oklahoma City, October 28-31, 1940.

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Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio, recently addressed a meeting of the Washington County Medical Society, held in Washington, Pa., on "The Problem of Ventricular Fibrillation and Cardiac Resuscitation."

## NEW LIFE MEMBERSHIP

Dr. Charles R. Drake, F.A.C.P., Minneapolis, Minn., became a Life Member of the American College of Physicians on September 30, 1940.

## GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged:

*Books*

- Dr. George Bachmann, F.A.C.P., Atlanta, Ga.—“The Essentials of Physiology and Pharmacodynamics,” 3rd edition;  
 Dr. Arlie R. Barnes, F.A.C.P., Rochester, Minn.—“Electrocardiographic Patterns—Their Diagnostic and Clinical Significance”;  
 Dr. Edward G. Billings (Associate), Denver, Colo.—“A Handbook of Elementary Psychobiology and Psychiatry”;  
 Dr. Nathan S. Davis, III, F.A.C.P., Chicago, Ill.—“The Injured Back and Its Treatment”;  
 Dr. Edgar Hull, F.A.C.P., New Orleans, La.—“Medical Nursing”;  
 Dr. Hugh Alister McGuigan, F.A.C.P., Chicago, Ill.—“Applied Pharmacology”;  
 Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, Okla.—“Tuberculosis and Genius”;  
 Dr. Wade W. Oliver, F.A.C.P., Brooklyn, N. Y.—“Fantasia”;  
 Dr. Edwin E. Osgood, F.A.C.P., Portland, Ore.—“A Textbook of Laboratory Diagnosis—With Clinical Applications for Practitioners and Students”;  
 Dr. Harold E. B. Pardee, F.A.C.P., New York, N. Y.—“Nomenclature and Criteria for Diagnosis of Diseases of the Heart”;  
 Dr. Albert M. Snell, F.A.C.P., Rochester, Minn.—“Diseases of the Gallbladder and Bile Ducts.”

*Reprints*

- Dr. George Bachmann, F.A.C.P., Atlanta, Ga.—16 reprints;  
 Dr. David M. Baltzan, F.A.C.P., Saskatoon, Sask.—1 reprint;  
 Dr. Harry S. Berman (Associate), Detroit, Mich.—1 reprint;  
 Dr. Nathan S. Davis, III, F.A.C.P., Chicago, Ill.—2 reprints;  
 Dr. Jason E. Farber (Associate), Buffalo, N. Y.—4 reprints;  
 Dr. Wayne Gordon (Associate), Billings, Mont.—6 reprints;  
 Dr. Barnett Greenhouse (Associate), New Haven, Conn.—1 reprint;  
 Dr. M. Coleman Harris, F.A.C.P., New York, N. Y.—1 reprint;  
 Dr. John N. Hayes, F.A.C.P., Saranac Lake, N. Y.—9 reprints;  
 Dr. Merritt H. Stiles, F.A.C.P., Philadelphia, Pa.—3 reprints;  
 Dr. James J. Waring, F.A.C.P., Denver, Colo.—13 reprints;  
 Dr. Winthrop Wetherbee, Jr. (Associate), Boston, Mass.—1 reprint.

## TWENTY-FIFTH ANNUAL SESSION OF THE COLLEGE

While the College celebrated its twenty-fifth anniversary in 1940, its Twenty-fifth Annual Session (no Annual Meeting was held during 1918) will be held in Boston, April 21–25, inclusive, 1941, with headquarters at the Hotel Statler.

The program for the morning Lectures and afternoon General Sessions is in charge of the President, Dr. James D. Bruce, Ann Arbor, Mich. Local arrangements and the program of Clinics, Panels and the Annual Banquet are under the General Chairman, Dr. William B. Breed, 264 Beacon Street, Boston. Local Committee

The University of Minnesota Medical School, Minneapolis, has announced that Dr. Arthur C. Kerkhof (Associate) and Dr. James B. Carey, F.A.C.P., have been promoted to Clinical Associate Professors of Medicine.

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Dr. Louis E. Viko, F.A.C.P., College Governor for Utah, Salt Lake City, spoke on "Etiology and Treatment of Hypertension," and Dr. Kenneth S. Davis, F.A.C.P., Los Angeles, Calif., spoke on "Limitation and Evaluation of the X-Ray in the Diagnosis of Disease of the Gallbladder" at the 37th annual meeting of the Nevada State Medical Association, held in Las Vegas, October 10-12, 1940.

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Dr. Harry Beckett Lang, F.A.C.P., Brentwood, N. Y., has been appointed superintendent of the Buffalo State Hospital.

Among the speakers at the meeting of the Northeast Texas District Medical Society, held in Texarkana, Tex., October 8, 1940, were:

Dr. Joseph F. McVeigh (Associate), Fort Worth, Tex.—"Some Observations on Malaria and Its Treatment";

Dr. Walter G. Reddick, F.A.C.P., Dallas, Tex.—"The Use of Sulfanilamide Derivatives in Acute Infections."

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Dr. William S. McCann, F.A.C.P., Rochester, N. Y., was one of the guest speakers at the 126th annual meeting of the Vermont State Medical Society, held in Rutland, October 10-11, 1940. Dr. McCann spoke on "Practical Considerations of the Newer Physiologic Studies of Renal Disease."

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The Committee on Postgraduate Instruction of the Arkansas Medical Society in coöperation with the University of Arkansas School of Medicine offered the ninth course in graduate instruction, October 16-17, 1940, at Little Rock. Dr. Hubert M. Parker (Associate), Kansas City, Mo., spoke on "Calcium Therapy, Indications and Contraindications" and "Management of Symptoms in Patients Who Have Had Several Laparotomies," and Dr. John N. Compton (Associate), Little Rock, Ark., spoke on "The Good and the Bad About Sulfanilamide and Related Drugs." during this course.

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On October 9, 1940, Dr. Lauritz S. Ylvisaker, F.A.C.P., Newark, N. J., spoke on "The Importance of Heart Disease" at a meeting of the Medical Society of the District of Columbia, held in Washington, D. C.

On October 30, 1940, Dr. Arthur C. Christie, F.A.C.P., Washington, D. C., addressed the society on "Diagnosis and Treatment of Cancer of the Pharynx."

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Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa., spoke on "Cardiology" at the semiannual meeting of the Medical and Chirurgical Faculty of the State of Maryland, held in Annapolis, October 9, 1940.

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Dr. Willard C. Rappleye, F.A.C.P., New York, N. Y., has been appointed Commissioner of Hospitals of New York City. Dr. Rappleye began his new work on October 2, 1940, having been granted a fifteen months' leave of absence from his position as Dean of the College of Physicians and Surgeons of Columbia University.

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Dr. Edward L. Bortz, F.A.C.P., Governor for Eastern Pennsylvania, Philadelphia, spoke on "Modern Treatment of the Diabetic" at a recent meeting of the Clearfield County Medical Society, held in Philipsburg, Pa.

Sevringhaus, Governor for Wisconsin, Madison, presided. Dr. Clarence H. Boswell, F.A.C.P., of Rockford, was Chairman of Arrangements.

The scientific program was as follows:

11:00 a.m.—Clinical Pathological Conference.

Dr. Harold D. Palmer, F.A.C.P., Pathologist, Rockford Hospital.

2:00 p.m.—“The Responsibility of the Internist to the Field of Industrial Medicine.”

Dr. Elston L. Belknap, F.A.C.P., Assistant Clinical Professor of Medicine, Marquette University School of Medicine, Milwaukee, Wis.

“The Clinical Importance of Various ‘Symptomless’ Anomalies of the Gastrointestinal Tract.” Dr. John A. Schindler (Associate), Monroe, Wis.

“Physical Aspects of Depressive Psychoses.” Dr. Carroll W. Osgood, F.A.C.P., Wauwatosa, Wis.

The group were the guests of the Rockford Hospital at luncheon, which was combined with an American College of Physicians Conference with Dr. Ernest E. Irons, Chicago, Regent of the College and Chairman of the American Board of Internal Medicine, as the guest speaker, his subject being “The Work of the American Board of Internal Medicine.”

Among other guests were Dr. James G. Carr, Second Vice President of the College, Dr. LeRoy H. Sloan, College Governor for northern Illinois, and Dr. N. S. Davis, III, F.A.C.P., all of Chicago.

At five o'clock in the afternoon a Reception, followed by dinner, was held at the Nelson Hotel. The meeting was enthusiastically attended by the Winnebago County Medical Society, as well as by approximately twenty-five Fellows and Associates of the College from Illinois and Wisconsin, making a total of approximately seventy-five.

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#### REGIONAL DINNER OF MISSOURI MEMBERS

On the evening of October 3, marking the end of the Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society, at Kansas City, a Dinner of the Fellows and Associates of the American College of Physicians was held under the Governorship of Dr. A. Comingo Griffith in honor of Dr. James G. Carr, Chicago, Second Vice President of the College. Twenty-three members were present. Dr. Carr made an interesting address and Dr. C. J. Barborka, F.A.C.P., Chicago, also gave an instructive talk. Thereafter there was general discussion concerning activities and objectives of the College. Members in attendance expressed the desire to have another meeting in the spring.

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The annual Pottenger homecoming day was held in the gardens of the Sanatorium at Monrovia, Calif., September 22, 1940. Every year the “Graduates,” or former patients, gather not only to renew their old acquaintances but to pay honor to Dr. Francis M. Pottenger. This year it was also to celebrate Dr. Pottenger's birthday (September 27). Personified in Earl Dunbar Meadows' poem as “The Mender of Broken Lives,” written in 1932 when the subject was elected president of the American College of Physicians, Dr. Pottenger as founder and head of the Pottenger Sanatorium was honored by more than three hundred patients, former patients, and friends.

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Dr. Horace K. Richardson, F.A.C.P., who has served for some time as Medical Director of the Austen Riggs Foundation, Stockbridge, Mass., recently resigned and has entered upon private practice of psychiatry at 11 E. Chase Street, Baltimore, Md.

he received a common school education, first working in the coal mines, later being employed by the Lehigh Valley Railroad Company as telegrapher, confidential clerk and train dispatcher.

Dr. Morgan was graduated from the old Medico-Chirurgical College of Philadelphia in 1897, where he was awarded the James M. Anders prize for the best report of medical clinics and excellence in medicine. He was officially connected with the Medico-Chirurgical College from 1898 until its merger with the University of Pennsylvania in 1916, in teaching and administrative positions, last holding chair of Associate Professor in Medicine.

He was elected to the Professorship of Applied Therapeutics, Medical Department, Temple University, in June, 1922, and served until June, 1928, when he was elected Professor of Clinical Medicine. He was made Emeritus Professor of Clinical Medicine in 1930.

A host of societies claimed his active membership. He was a member and past president of the Philadelphia County Medical Society; the Medical Society of the State of Pennsylvania, and the Welsh Society of Philadelphia; he was a member of the Philadelphia Clinical Association, the Aesculapian Club, the Physicians' Motor Club, the Union League of Philadelphia, the Royal Arcanum, and the Pennsylvania State Board of Medical Education and Licensure, 1931-1936. He was a Fellow of the College of Physicians of Philadelphia and a Fellow of the American College of Physicians since 1922.

Dr. Morgan was Attending Physician to the Tuberculosis Department of the Philadelphia General Hospital since 1905, Lecturer to the Nurses' Training School for several years, and a member of the board for selection of interns for eight years. He was Physician-in-Chief and Medical Director of the Frankford Hospital for eight years and Lecturer to the Nurses' Training School.

He was Consulting Internist to the Chambersburg, Nanticoke State, and Community (Quakertown) Hospitals, Eastern State Penitentiary, and formerly the State Hospital for the Insane at Norristown, Pa.

Dr. Morgan was a member of the Methodist Episcopal Church since early boyhood, serving as trustee and treasurer of East Park Church for eleven years.

He served in the Medical Corps, U. S. Army, from July 3, 1917, to December 27, 1918. He was President of the Board of Examiners for heart and lungs at the several stations where he served.

Dr. Morgan collaborated with Professor James M. Anders in revision of several editions of "Anders' Practice of Medicine." He was also Associate Editor of *The Pennsylvania Medical Journal*, and author of numerous monographs on various topics and subjects in medicine.

During the past twenty years his practice had been restricted to internal medicine, consultation, hospital, and teaching.

Dr. Morgan was married June 24, 1903, to Laura Blake, who died

Among the guest speakers at the 90th annual meeting of the Medical Society of the State of Pennsylvania, which was held in Philadelphia September 30 to October 3, 1940, were:

Dr. Tom Douglas Spies, F.A.C.P., Cincinnati, Ohio—"Recent Advances in Vitamin Therapy";

Dr. Thomas B. Magath, F.A.C.P., Rochester, Minn.—"Hydatid Disease in North America."

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The American Public Health Association held its 69th annual meeting in Detroit, Mich., October 6-11, 1940. Among the guest speakers at this meeting were:

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.—"Some Important Factors in the Etiology of the Anemias";

Dr. John B. Youmans, F.A.C.P., Nashville, Tenn.—"An Assessment of the Nutrition of a Rural Population in Tennessee";

Dr. Julius H. Hess, F.A.C.P., Chicago, Ill.—"Essentials in the Care of Premature Infants";

Dr. George Baehr, F.A.C.P., New York, N. Y.—"Public Health Importance of the Intravenous Drip Method for Treatment of Syphilis."

Dr. Thomas Parran, F.A.C.P., Surgeon General, U. S. Public Health Service, presided at a special afternoon session on "The Control of Venereal Diseases in a National Defense Program." The speakers at this special session included Major General James C. Magee, F.A.C.P. (MC), USA, Surgeon General, U. S. Army, and Rear Admiral Ross T. McIntire, F.A.C.P. (MC), USN, Surgeon General, U. S. Navy.

Dr. Waller S. Leathers, F.A.C.P., Nashville, Tenn., was installed as president of the Association and spoke on "Public Health in National Defense."

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At a meeting of the Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Sanatorium Association in St. Paul, Minn., October 2-4, 1940, Dr. John H. Skavlem, F.A.C.P., Cincinnati, Ohio, presided at a roentgen-ray conference. Among those who presented papers at this meeting were:

Dr. Bruce H. Douglas, F.A.C.P., Detroit, Mich.—"The 4×5 Film in Case Finding";

Dr. David O. N. Lindberg, F.A.C.P., Decatur, Ill.—"Relative Usefulness of 35 Mm. Films in Case Finding."

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Dr. George Argale Harrop, F.A.C.P., Princeton, N. J., was one of the speakers at a seminar sponsored by the Jefferson County (Ala.) Medical Society in Birmingham, September 16-17, 1940.

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The Polk County (Iowa) Medical Society opened a series of postgraduate programs in Des Moines, September 18, 1940. Dr. Clifford J. Barborka, F.A.C.P., Chicago, Ill., was one of the speakers at this opening meeting. His subject was "Food in the Practice of Medicine."

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., spoke on the "Relation of Physiology to Modern Medicine" at another of these postgraduate programs on November 20.

This society has announced that Dr. David P. Barr, F.A.C.P., St. Louis, Mo., will speak on "The Making of a Diagnosis" on March 19, 1941, and Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., will speak on "Endocrinology in General Practice" on May 21, 1941.

while in Davidson. After he relinquished practice, he spent his remaining days in Davidson, N. C., where he died from pneumonia at the Charlotte Sanatorium on October 14, 1940.

As stated in an editorial in the Charlotte Observer; "Dr. Munroe was respected to an unique degree by his professional associates for his medical learning, and his progressive and adventurous enterprise; he was none the less held in eminent regard by the public because of his strong and self reliant manhood, the generosity of his impulses, his contagious good humor, and rugged, clean and unsullied honesty."

His bibliography embraces many valuable papers, relating largely to his chosen specialty of nervous and mental diseases, the last of which was published as late as 1936, when Dr. Munroe was 79 years of age.

CHARLES H. COCKE, M.D., F.A.C.P.,  
Governor for North Carolina

### DR. EVERETT ELDRIDGE WATSON

Dr. Everett E. Watson, Associate, of Salem, Va., was born August 16, 1889, at Hillsville, Va., died August 4, 1940, of pulmonary tuberculosis of which he had been a chronic sufferer for many years.

He graduated at the University College of Medicine in 1912. He developed tuberculosis during his third year in Medical School which necessitated his resting a year to take the cure. After his graduation he went to Saranac Lake for treatment and postgraduate work. He was Assistant Resident Physician at Catawba Sanatorium from September 1913 until May 1914. In May 1914 he opened the Mount Regis Sanatorium at Salem, Virginia, a fifty bed hospital for the treatment of tuberculosis. He was Medical Director there until his death.

Dr. Watson was a past president of the Roanoke Academy of Medicine. He was a member of the Virginia State Medical Society, American Medical Association, American Association for Thoracic Surgery, National Tuberculosis Association, Southern Medical Association, Southwest Virginia Medical Society; Honorary Member, West Virginia Medical Society; author of numerous publications on the diagnosis and treatment of tuberculosis; Consulting Specialist, U. S. Veteran's Bureau; Surgeon, Norfolk and Western Railroad, and one of the pioneers in pneumothorax therapy in the state.

Personally, Dr. Watson was a delightful individual. He was exceedingly popular in college; a member of the Omega Upsilon Phi Fraternity. This popularity followed him throughout life. A lovable character, a real physician will be missed by a host of friends but chiefly in the field of tuberculosis.

His wife, Mrs. Patience P. Watson and one son, Dr. John C. Watson, survive him.

C. L. HARRELL, M.D., F.A.C.P.,  
Norfolk, Virginia

Dr. Harvey G. Beck, F.A.C.P., Baltimore, Md., addressed the Lawrence County Medical Society at their recent meeting in New Castle, Pa. His subject was "Chronic Illness Resulting from Carbon Monoxide."

The Association of Military Surgeons of the United States held its 48th annual meeting in Cleveland, Ohio, October 10-12, 1940, under the presidency of Major General Charles R. Reynolds, F.A.C.P. (MC), USA, Retired, Harrisburg, Pa. Among the speakers at this meeting were:

Rear Admiral Ross T. McIntire, F.A.C.P. (MC), USN, Surgeon General, U. S. Navy,—“Selection of Men Adapted for Special Fields”;

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio—“Chemotherapeutic Developments Since the Last War”;

Dr. Ernest P. McCullagh, F.A.C.P., Cleveland, Ohio—“Differential Diagnosis of Neurocirculatory Asthenia (Soldier's Heart) and Results in 152 Denervations of the Adrenal Glands in Treatment of Neurocirculatory Asthenia.”

The Medical Society of the District of Columbia held its annual scientific assembly in Washington, October 15-17, 1940. The subject of this assembly was cardiovascular renal diseases. Among those who spoke at this meeting were:

Dr. Raymond Hussey, F.A.C.P., Baltimore, Md.—“Some Interesting Electrocardiographic Interpretations”;

Dr. Walter A. Bloedorn, F.A.C.P., Washington, D. C.—“Recognition and Treatment of the Various Forms of Pericarditis”;

Dr. Wallace M. Yater, F.A.C.P., Washington, D. C.—“Diseases of the Aorta”;

Dr. George Louis Weller, Jr., F.A.C.P., Washington, D. C.—“Surgical Shock and Circulatory Failure”;

Dr. Thomas S. Lee, F.A.C.P., Washington, D. C.—“Hypertensive Heart Disease”;

Dr. Edward Weiss, F.A.C.P., Philadelphia, Pa.—“Renal Involvement in Hypertensive Vascular Disease”;

Dr. Maurice C. Pincoffs, F.A.C.P., Baltimore, Md.—“Cardiac Aspects of Chronic Nephritis”;

Dr. Howard B. Sprague, F.A.C.P., Boston, Mass.—“Clinical and Electrocardiographic Findings in the Aging Heart”;

Dr. James Edwin Wood, Jr., F.A.C.P., Charlottesville, Va.—“Diagnosis and Treatment of Cardiac Arrhythmias”;

Dr. James Alexander Lyon, F.A.C.P., Washington, D. C.—“Failure of the Left and Right Sides of the Heart”;

Dr. Joseph B. Wolffe (Associate), Philadelphia, Pa.—“Recognition and Management of Cardiac Neurosis”;

Dr. Edwin Cowles Andrus, F.A.C.P., Baltimore, Md.—“Acute Coronary Thrombosis”;

Dr. Irving Sherwood Wright, F.A.C.P., New York, N. Y.—“Diagnosis and Conservative Treatment of Peripheral Vascular Diseases.”

Dr. Samuel F. Rosen, F.A.C.P., Savannah, Ga., spoke on “Occupational Dermatoses” at the 3rd annual meeting of the Georgia Association of Industrial Surgeons, held in Atlanta, September 25, 1940.

Dr. John H. Musser, F.A.C.P., New Orleans, La., has been appointed president of the Louisiana State Board of Health to serve on a part time basis until January, during the reorganization of the board.



eases of the Heart," "Basic Diets" and "Diabetic Diets with a Universal Diabetic Diet List." He also was an authority on genealogy and wrote a history of his own family. His clubs included the University and Pleiades and he was a member of Phi Beta Kappa and Chi Psi fraternities.

Unmarried, Dr. Cornwall leaves a sister, Miss Eloise Cornwall of Mount Morris, N. Y.

CHARLES F. TENNEY, M.D., F.A.C.P.,  
Governor for Eastern New York

### DR. GEORGE BARROW WORTHINGTON

Dr. George Barrow Worthington, born in Garston, England, August 24, 1877; died at his home in San Diego, Calif., August 12, 1940. He graduated from the Cooper Medical College, now Stanford University School of Medicine, in 1904, and pursued postgraduate work in later years at the New York Polyclinic Medical School, New York Post-Graduate Medical School and the University of California.

Dr. Worthington was formerly Coroner's Physician and County Health Officer, San Diego County, and City Health Officer of San Diego. From 1916 to 1918 he was chief surgeon of the Hercules Powder Company. In 1916 he served as an officer in the U. S. Army at the Mexican Border, and during the World War he served at Camp Kearney.

Dr. Worthington was formerly secretary, formerly president and formerly editor of the *Bulletin* of the San Diego County Medical Society. He was a member of the California State Medical Society, Southern California Medical Association and the American Medical Association. He had been retired from active practice for the past few years because of ill health. He had been a Fellow of the American College of Physicians since 1930.

"Kindly, gracious and understanding, he was always a teacher—always endeavoring to help the interne with his problems as well as to aid the patient through his knowledge and skill. A dreamer—yet a practical and accomplished physician—he stands out as the rare example of the type of man who could make an internship worth something to young men during their period of training."—*The Bulletin*, San Diego County Medical Society.

The Aero Medical Association of the United States held its 12th annual meeting in Memphis, Tenn., October 25-27, 1940. Among the speakers were:

Dr. Walter M. Bartlett, F.A.C.P., Benton Harbor, Mich.—“The Use of Combined Electrocardiography, Electrosthethography and Cardioscopy in the Early Recognition of Heart Disease as Especially Applied to the Selection of Pilots”;

Dr. Edward J. Van Liere, F.A.C.P., Morgantown, W. Va.—“The Effect of Anoxia on the Digestive Processes.”

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Among the speakers at the 51st annual meeting of the Association of American Medical Colleges held at the University of Michigan, Ann Arbor, October 28-30, 1940, were:

Dr. James D. Bruce, F.A.C.P., Ann Arbor, Mich.—“The Expanding Phases of Postgraduate Medical Education”;

Dr. Willard C. Rappleye, F.A.C.P., New York, N. Y.—“The Internship”;

Dr. Linn J. Boyd, F.A.C.P., New York, N. Y.—“Some Observations on the Teaching of Pharmacology”;

Dr. George E. Wakerlin, F.A.C.P., Chicago, Ill.—“A Plan for the Protection of Medical Research.”

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Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, Ill., was presented with one of the annual awards of merit of the American Congress of Physical Therapy at its annual meeting in Cleveland, Ohio, September 2-6, 1940.

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Among the speakers at the annual meeting of the American Dietetic Association, held in New York, N. Y., October 20-24, 1940, were:

Dr. Eugene F. Du Bois, F.A.C.P., New York, N. Y.—“Fewer and Better Diets”;

Dr. Norman H. Jolliffe, F.A.C.P., New York, N. Y.—“Recent Advances in Clinical Applications of the B Vitamins”;

Dr. Abraham H. Aaron, F.A.C.P., Buffalo, N. Y.—“Diet in Diseases of the Digestive Tract”;

Dr. Herbert Pollack (Associate), New York, N. Y.—“What the Dietitian Should Know About Clinical Laboratory Methods.”

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Dr. Ralph C. Matson, F.A.C.P., of Portland, Oregon, was recently made an Honorary Member of the Sociedad Mexicana de Estudios Sobre la Tuberculosis, Mexico, D. F.

In the society's official journal, “Revista Mexicana de Tuberculosis,” May and June 1940 issue, appears an editorial regarding Dr. Matson, his work and contributions to the treatment of tuberculosis. In the same issue is an article by Dr. Matson on “Further Experiences with Intrapleural Pneumolysis.”

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## OBITUARIES

### DR. ARTHUR CARADOC MORGAN

Dr. Arthur Caradoc Morgan, former President of the Philadelphia County Medical Society and the Medical Society of the State of Pennsylvania, died early Monday morning, October 21, 1940, in Temple University Hospital, Philadelphia, Pa.

Dr. Morgan was born in Lost Creek, Pa., November 14, 1869, where

The familial feature of the disease was very definite, being present in 92.6 per cent of the group. There were 12 families represented by our 28 patients. The disease was passed on equally by male or female. In two families, the disease could be traced through three generations. There were only two cases which did not show a familial feature, yet we were reluctant to classify them as "acquired" types of the disease because circumstances prevented any detailed study of other members of their families. As a result, we have almost reached the conclusion that the so-called "acquired," non-hereditary form of the disease is non-existent. We have seen 7 cases, not included in this report, that might have been considered as "acquired" types because of their marked and persistent anemia, acholuric jaundice, reticulocytosis, bone marrow hyperplasia and gross splenomegaly. However, they differed from typical chronic familial hemolytic jaundice in that there was no evidence of the familial tendency, the blood picture was characterized by a macrocytic anemia, a leukopenia and an absence of spherocytosis, and the fragility of the erythrocytes, though slightly altered, was not definitely increased. Furthermore, splenectomy failed to bring about any improvement in these cases either from a clinical or hematological standpoint.<sup>2</sup>

The etiology of chronic familial hemolytic jaundice remains obscure. The various theories of the primary mechanism at fault resolve about whether the spleen, through its abnormal phagocytic action on the red blood cell, is the major pathologic agent,<sup>3</sup> or whether the bone marrow produces an abnormally thick, spherical, fragile red cell which is more susceptible to disruption and fragmentation than the ordinary erythrocyte.<sup>4</sup> Others<sup>5</sup> believe that both factors operate in that the spleen causes further distortion of an already abnormal red cell. Whatever the true cause, the clinical fact remains that the patient obtains a symptomatic "cure" following removal of the over-active spleen, even though tell-tale signs in the blood picture persist.

#### CLINICAL MANIFESTATIONS

After observing a group of these patients for some length of time, one cannot help being impressed by the variability of the symptoms either in the same patient at different times, or in different members of the same family. Therefore, it is difficult to place any single patient in a classification of acute, chronic, and latent types of the disease. In this series of cases, there were only two purely latent cases, 52 and 63 years of age, both members of the same family in which four active cases of three generations were present. These two were discovered in a routine investigation of apparently "well" members. The majority of cases ran a chronic course over a period of years interrupted by a variable number of acute exacerbations and spontaneous remissions, with or without complications. The duration of symptoms for the group averaged over 13 years. The earliest and most common complaint experienced by the patient was usually

February 10, 1931. He is survived by one daughter, Margaret, a graduate of Bryn Mawr College.

Dr. Morgan's death marks the passing of one of America's most distinguished physicians and teachers. Through his death the American College of Physicians has lost one of its most loyal and valuable members.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

### DR. JOHN PETER MUNROE

Dr. John Peter Munroe was born in Oak County, North Carolina, March 29, 1857, the youngest of six sons, all of whom attained distinction in different fields of endeavor. He received his A.B. degree from Davidson College in 1882, and his M.D. from the University of Virginia in 1885, after which he served an internship in St. Luke's Hospital, Richmond, under Dr. Hunter McGuire.

After three years' practice in Durham, he returned to Davidson College as Director of the Medical Department of that institution, which was founded by Dr. Paul Barringer in 1887. This school was incorporated as the North Carolina Medical College in 1893, being moved to Charlotte in 1907. During this period Dr. Munroe was President of the College as well as Professor of Mental and Nervous Diseases, although his activities frequently embraced teaching in every department of the College. The North Carolina Medical College merged with the University College of Medicine in Richmond, Va., in 1914. Since then until his retirement a few years ago Dr. Munroe practiced medicine in Charlotte, specializing in nervous diseases and internal medicine. The span of Dr. Munroe's medical activities extended from the era of saddle bags to our present period of advancing knowledge and improved facilities for diagnosing and treating the sick. He was abundantly equipped with the spiritual temperament and intellectual perceptiveness demanded of these periods, and ever kept abreast of modern developments in medicine.

He was a great leader not only in his city but also in his State, and was largely instrumental in the development of the Presbyterian Hospital and the Charlotte Sanatorium, two leading institutions of healing and treatment in North Carolina's largest city. His vision and fine enthusiasm for advanced medicine stimulated and encouraged his associates who have accorded him the title of Nestor of his profession in his part of the world.

Dr. Munroe became a member of the American College of Physicians in 1920; his other medical societies embraced the Mecklenburg County Medical Society, the North Carolina Medical Society, the Tri-State Medical Society, the Southern Medical Association, and the American Medical Association. He was President of the first three named societies. He was given honorary degrees of D.Sc. by Duke University and LL.D. by Davidson College. Dr. Munroe was a devoted member of the First Presbyterian Church and for years served it as an elder. He was also director of music

The association of chronic familial hemolytic jaundice with secondary pigment cholelithiasis is well known. This complication, present in 63 per cent of 14 studied cases, probably develops as a result of the persistent increased bilirubin content of the blood producing an increased load on the excretory function of the liver and gall-bladder. The calculi were usually found to be of the soft pigment type contained in a comparatively normal, thin-walled gall-bladder. If biliary colic is the first event in the clinical history, the primary disease may be over-looked. Though recognized as hemolytic jaundice, two patients in this group whose gall-bladders were first removed, continued to show little or no improvement in their jaundice or anemia; one has since been cured by splenectomy. It would seem advisable, therefore, that unless common duct obstruction is present, the spleen should always be removed first and at a later date, if necessary, biliary surgery performed. Of our 13 splenectomized patients, only 3 have had to return for removal of their gall-bladders. In one of our recent cases, we performed a cholecystotomy at the time of splenectomy but did not succeed in relieving the patient of his attacks of biliary colic. Further attempts of this type should be made in such patients with gall stones in order to avoid, if possible, a second major operative procedure.

In our experience, pregnancy acted as an additional complication in the course of chronic familial hemolytic jaundice. Since this disease is so active in the child-bearing age group, any further demand or load thrown on the hematopoietic system such as occurs in pregnancy may well serve to "light up" a latent case or cause an acute exacerbation in a chronic form of the disease. Pregnancy occurred 19 times in 7 of our patients and in 52 per cent of these instances the pregnancies had some deleterious effect on the course of the disease. Not only was the anemia made more pronounced, but miscarriages and premature deliveries were more frequent. On the other hand in 23 splenectomized women, Mussey and Blakley<sup>8</sup> have shown no gross alteration in the course of pregnancy, confinement or puerperium. In passing it is of interest that in two of our pregnancy cases, the cord blood was studied at the time of delivery but the fetal erythrocytes failed to show any abnormality of fragility, and in neither case did icterus neonatorum develop.

#### LABORATORY FINDINGS

The peculiarly distinctive and characteristic changes in the blood of patients with chronic familial hemolytic jaundice are well known. The severity of the anemia varied with the activity of the hemolytic or destructive phase of the erythrocytic equilibrium. For the most part, the anemia was of moderate degree. The number of erythrocytes averaged 3,840,000 cells per cubic millimeter and the amount of hemoglobin 73.0 per cent (12.4 grams). With the occurrence of acute crises the red blood cells may decrease sharply to as low as one million or even less. Typical of chronic familial hemolytic jaundice, the globule or sphere-shaped microcytes were

## DR. FRANK VAN DER BOGERT

Dr. Frank van der Bogert, F.A.C.P., Schenectady, N. Y., died September 24, 1940. Dr. van der Bogert was born in Schenectady in 1873. He received his A.B. degree from Union College in 1895 and his M.D. degree from the University of Pennsylvania School of Medicine in 1900.

Dr. van der Bogert had been in charge of the Department of Pediatrics, Ellis Hospital, Schenectady, for the past twenty-five years, and at the time of his death, he was Consultant in Pediatrics there. He was an Associate in Pediatrics at the Albany Medical School until 1934, and had been special lecturer in pediatrics at this school since 1937. He was a Visiting Pediatrician to the Schenectady City Hospital, and since 1933 he had been Chairman of the Medical Advisory Committee of the Schenectady Public Schools.

Dr. van der Bogert was a member and past president of the Schenectady County Medical Society and the Central New York Pediatric Club. He had been Chairman of the Pediatric Section of the Medical Society of the State of New York, a Fellow of the New York Academy of Medicine and the American Academy of Pediatrics and the American Medical Association. He was one of the early Fellows of the American College of Physicians, having been elected in 1916.

Dr. van der Bogert was the author of about forty papers and case reports on pediatrics. He had the unusual hobby of collecting corks.

CHARLES F. TENNEY, M.D., F.A.C.P.,  
Governor for Eastern New York

## DR. EDWARD EVERETT CORNWALL

Dr. Edward Everett Cornwall was born in Buenos Aires, Argentina, S. A., July 2, 1866, the son of Dr. Nathaniel Cornwall, a dentist there. He was a descendant of John and Priscilla Alden. He died on October 8, 1940.

He graduated from Columbia University College of Physicians and Surgeons, 1890; Interne and House Physician, Presbyterian Hospital, New York City, 1890-92. From 1906 until his death Dr. Cornwall was on the staff of the Norwegian Lutheran Deaconesses' Home and Hospital. He also served on the staffs of Bethany Deaconess, St. John's, Brooklyn Eye and Ear and Williamsburgh Hospitals, all in Brooklyn, the Broad St. Hospital, Manhattan, and the Southside Hospital, Bayshore, L. I. He was a member of Kings County Medical Society, New York State Medical Society and the Pan American Medical Association; he was a member and former president of Brooklyn Society of Internal Medicine and Greater New York Medical Association; Fellow and former member of the House of Delegates, American Medical Association; former member of council, American Therapeutic Society; one of the incorporators and former councilors of the American College of Physicians. He was a frequent contributor to leading medical journals and was the author of "Clinical Treatise on Dis-

gone splenectomy. The youngest patient was 4 years and the oldest 58 years of age.

In capable surgical hands, splenectomy has proved to be a relatively simple operative procedure in spite of working with sub-par patients. Adhesions about the spleen were relatively infrequent. Various types of anesthetics were purposely tried. In typical cases, neither transfusions nor any other anti-anemic therapy was necessary either before or after surgery. There were no postoperative complications or fatalities such as were observed in another group of 7 patients splenectomized either for Banti's disease or chronic refractory anemia.<sup>2</sup> The convalescence was surprisingly rapid with disappearance of the jaundice within a few days. The reticulocytes returned to normal numbers within the first postoperative week.

We have recently reported<sup>2</sup> a modified support of Doan's observations<sup>6</sup> that the improvement in these patients begins with changes in the blood that occur during splenectomy while the patient is still in the operating room. It is our opinion that these immediate blood changes were the result of an auto-transfusion effect into the peripheral circulation from the surgical manipulation of the enlarged splenic reservoir. That splenectomy caused such an immediate and dramatic change in the blood has not yet been recognized sufficiently and should be of some clinical importance in considering the surgical risks of patients with acute hemoclastic crises. In such cases which do not respond to conservative treatment, Doan<sup>10</sup> has advised emergency splenectomy with excellent results. Since we have not yet felt it necessary to perform an "emergency" splenectomy, we have not had the opportunity to observe the blood response in this type of patient. It would seem, however, that the addition of postoperative transfusions in such acutely ill patients would greatly shorten the convalescent period and serve to help prevent or modify postoperative complications.

In our hands, iron and liver therapy have been of no value to the patient with chronic familial hemolytic jaundice, either in improving the anemia or in preventing the occurrence of complications. Those patients who have elected such conservative treatment, continue to be subject to the state of chronic invalidism and to the risk and uncertainty of acute exacerbations of the disease. It is our practice, therefore, to recommend splenectomy for those individuals with active clinical manifestations with or without complications irrespective of age and independent of the severity of the disease. In such patients, the chronicity of symptoms and the uncertainty as to the occurrence of serious complications more than offset the slight risk of operation especially in view of the good health which the latter offers the patient.

#### CONCLUSIONS

1. A brief, clinical analysis of 28 cases of chronic familial hemolytic jaundice is presented together with a discussion of the characteristic blood changes.

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## HEMOLYTIC JAUNDICE: A CLINICAL ANALYSIS OF 28 CASES\*

By JOHN C. SHARPE, M.D., *Omaha, Nebraska*

FROM the maze of confused terminology and the many classifications of the vague group of blood diseases called hemolytic anemia, only chronic familial hemolytic jaundice stands out as a definite symptom-complex in which the diagnosis is exact and the treatment satisfactory. The disease, though not common, is of sufficient frequency to excite suspicion and warrant careful consideration in any patient with unexplained anemia with or without jaundice. This is evidenced by our group of 28 cases that have been seen at the University Hospital in the past three years. It is our purpose to present a brief clinical analysis of these cases together with their characteristic blood changes, the various complications and the indications for and the results of treatment. The study presents a fairly accurate cross section of the voluminous literature on the subject. The term chronic familial hemolytic jaundice will be used in preference to such varied names as hemolytic jaundice, hemolytic anemia, acholuric icterus, acholuric ictero-anemia, hemolytic splenomegaly, splenic anemia or chronic infectious anemia with splenomegaly. We may define chronic familial hemolytic jaundice as a chronic micro-spherocytic anemia, characterized by increased fragility of the red cells, reticulocytosis, acholuric icterus and splenomegaly.<sup>1</sup>

### ETIOLOGY

Chronic familial hemolytic jaundice is a disease of all ages and of either sex. In our 28 cases there were 11 males and 17 females; their ages varied from 3 to 63 years. The age at which symptoms first appeared, however, was usually within the first two decades of life. Occasionally, sub-clinical evidence of the disease would remain latent and unsuspected for many years and be discovered only if the individual or some other member of the family was found to be an active clinical case.

\* Read at the New Orleans meeting of the American College of Physicians, March 30, 1939.

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# A STUDY OF SYPHILIS OF THE AORTA AND AORTIC VALVE AREA \*

By CHARLES F. NICHOLS, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

THE widespread interest now manifested in the early diagnosis and adequate treatment of syphilis would seem to justify once again a review of the tragic effects of this disease on the cardiovascular system. The term "cardiovascular syphilis" is widely used but, in order properly to understand the evolution of the disease, the term "vascular syphilis" would be preferable. Excepting only cerebral vascular syphilis and rare involvement of other vessels (as the innominate artery), vascular syphilis in the great majority of cases resolves itself into syphilis of the aorta. Primary involvement of the aortic valves and heart, although it does occur, is rare. Syphilis of the aorta must be recognized as a progressive pathological process. The possibility that the aorta is invaded early by the *Treponema pallidum* in all untreated cases and, as many believe, even in the first few weeks of the disease, calls for the application of early and prolonged treatment which will effect sterilization and a biological cure. Any campaign which fails to appreciate that all the serious late manifestations of this disease originate in the early stage of infection is doomed to failure. The treatment of the disease as it reaches us in the wards of our large general hospitals seems almost hopeless, and it may well be again repeated of syphilitic aortitis that "the initial stage clinically is already a relatively advanced stage anatomically."<sup>1</sup>

## PATHOLOGY

Syphilitic aortitis, with rare exception, begins in the supra-sinus aorta just above the aortic valve. It may remain localized as an uncomplicated aortitis; or, more often, it extends downward to involve the commissures and valves in a rather typical pattern. The ascending aorta and the aortic arch are abundantly supplied with lymphatics, and the invasion of the aorta occurs through these lymphatics accompanying the vasa vasorum. The degenerative process in the media and the proliferative changes in the adventitia are well understood. There is a destructive process in the elastic and connective tissue of the media, plus a reparative fibrosis, resulting in scarring and deformity of a varying degree. The intimal thickening and retraction often result in characteristic ridge-like scarring. Various complications arise from the spread of this simple aortitis, the speed of the process varying tremendously and depending upon defense mechanisms, the nature of which is still an unsolved problem. The microorganism of syphilis, like that of tuberculosis, possesses the remarkable ability to sur-

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From the Medical Service of Dr. Thomas F. Klein, The Philadelphia General Hospital.

that of undue fatigue. At times this feature was so marked that the individual was more or less invalidated by it. Such symptoms as dyspnea, palpitation and dizziness were often intermittently present depending on the severity of the anemia.

Jaundice may occasionally be the first symptom noted or it may be entirely absent during the course of the disease. When present, it was never very intense, the skin color varying from that of a muddy sallowness to a daffodil tint. The bilirubinemia, though varying in degree at different times, was found persistently above normal. Though there seemed to be a rough parallelism between the degree of anemia and the amount of jaundice, this association was not always observed. Perhaps Doan's<sup>6</sup> explanation that jaundice depends on the excretory capacity of the liver cells, irrespective of the severity of the anemia, may better explain its clinical presence or absence.

Splenomegaly was characteristically present in all but our two latent cases. According to Gänsslen,<sup>7</sup> enlargement of the spleen is not essential for diagnosis provided the other features of the disease are present. The degree of splenic size varied at different times in the same individual and, in our experience, bore no relation to the severity of the case. On several occasions, the discovery of a palpable spleen during an initial physical examination led the physician to further investigation and to the correct diagnosis.

### COMPLICATIONS

During the course of chronic familial hemolytic jaundice, various complications of the disease developed that often completely altered the clinical picture. These complications were chiefly of two types, the first that of acute episodes of blood destruction, and the second of more chronic nature leading to the formation of gall stones.

Acute hemoclastic crises occurred at irregular intervals with no apparent explanation. The attacks were characterized by a sudden onset of upper abdominal pain, nausea, vomiting and fever, accompanied by marked weakness with an intensification of jaundice and pallor, an increasing enlargement of the spleen, and a sharp drop in the blood count. During the attacks, the degree of jaundice and the size of the spleen would vary from hour to hour. These severe and at times alarming episodes occurred 17 times in 10 of our patients. In one family, for no apparent cause, such hemoclastic crises occurred in four members within an interval of one week and resulted in one death. In another family within two weeks of each other, a mother and four year old daughter both had acute severe crises with the red cells falling to just under one million before spontaneous recovery slowly took place. After leaving the hospital, one other case died in an acute crisis in spite of repeated transfusions and deep roentgen-ray therapy over the spleen. In no instance has such a crisis occurred subsequent to splenectomy.



observed in the stained smear of each case. Using the Wintrobe hematocrit, the small diameter yet increased thickness of the red cells frequently resulted in giving fairly normal cell volume readings. In addition, the mean corpuscular hemoglobin concentration was significantly increased.

Evidence of bone marrow hyperplasia was reflected by the characteristic increased number of reticulocytes in the peripheral circulation. The number of reticulocytes varied in different cases from 2.0 to 34.2 per cent, with a group average of 10.7 per cent. Except during an acute crisis, there was no significant relation between the degree of reticulocytosis and the grade of anemia. Bone marrow biopsies on 6 cases further emphasized the increased demand for new red blood cells to compensate for the excessive cell destruction in the spleen. In each sternal biopsy, marked erythrocytic hyperplasia chiefly of the normocytic type was found.

Increased fragility of the erythrocytes to hypotonic salt solution was found on repeated examinations during many different stages of activity of the disease. The increased fragility is, of course, pathognomonic of the disease. There are several reports in the literature,<sup>7,9</sup> as well as one of our cases, in which the fragility was normal before, yet persistently increased after splenectomy in spite of the disappearance of jaundice and anemia. In our group of patients the average percentage concentration of the salt solution of the beginning of hemolysis of the erythrocytes was 0.61 per cent and the average at complete hemolysis was 0.36 per cent. Haden<sup>4</sup> has recently pointed out that the spherocytes of hemolytic jaundice are similar to the globular shape of normal erythrocytes just before the point of hemolysis after having been placed in hypotonic salt solution. He feels there is a direct relation between the increased thickness of the cells found in hemolytic jaundice and the increased fragility.

The number of white blood cells was normal in 16 cases, and moderately elevated, from 10- to 20,000, in 12 cases. A shift to the left of the neutrophilic series with appearance of a small number of myeloblasts and myelocytes frequently occurred during the acute hemoclastic crises. Also, at the time of severe grades of anemia, polychromasia and normoblasts were often observed.

It was obvious that the patients' jaundiced appearance was caused by the consistently elevated bilirubin content of the blood. With the normal blood icterus index ranging from 3 to 5 units, these patients' indices varied from 4 to 50 units with an average for the group of 19 units. Furthermore, the Van den Bergh test was indirectly positive, the stools were highly colored with bile, and urobilin was present in the urine. Various other laboratory studies were all found within normal limits.

#### TREATMENT

The value of splenectomy in chronic familial hemolytic jaundice is, at the present time, unquestioned. In this series of 28 patients, 13 have under-

The diagnosis of uncomplicated syphilitic aortitis is frequently difficult and in many instances impossible. We are constantly seeing at post mortem typical examples of syphilitic aortitis that were clinically silent. Many patients do not consult a physician until the disease has produced structural defects in the aorta or at the aortic valves.

In necropsies on a large number of young negro soldiers in France during the War, a small patch of syphilitic aortitis was a common finding. It had apparently produced no symptoms. Judging from the ages of these men and of the group coming under observation with symptoms referable to aortitis, there must be a long period of latency, 10 to 20 years of silent progress, during which death often occurs from other causes.

One seldom sees simple aortitis in the wards of a large charity hospital, or at least it is seldom diagnosed. The writer has examined many syphilitics in the early years of their disease and could find no evidence upon which to base a diagnosis of simple luetic aortitis. Symptoms other than those from aneurysm or myocardial failure were rarely noted. Scott<sup>3</sup> further observed:

The mere presence of a patch of syphilitic inflammation in the aorta is not the only factor concerned in the production of symptoms. The nervous organization of the individual and the receptivity of the nervous system to afferent visceral impulses play an outstanding rôle. If we are then to diagnose syphilitic aortitis before it has produced gross anatomical changes in the aorta or in the aortic valves, the diagnosis must be largely one of inference, strikingly so in patients who have no symptoms. It is well to remember then that latent syphilis more frequently involves the aorta than any other viscus, that syphilis may be present in the aorta for more than forty years and the patient present no signs or symptoms of disease.

This was strikingly illustrated by a recent autopsy. Death had occurred at the age of 70, due to prostatic obstruction; yet final examination revealed a simple diffuse aortitis involving nearly the whole aortic tube. This process must have been symptomless and latent for more than four decades.

Studies from a large number of clinics give varying figures as to the frequency of syphilitic aortitis. It would appear that it occurs in from 4 to 7 per cent of general hospital autopsies, that it is the undoubted etiological factor in 20 to 25 per cent of organic heart disease, and is found in from 60 to 80 per cent of syphilitics. Stokes<sup>4</sup> believes that the incidence of cardiovascular syphilis, insofar as available figures indicate, is showing a downward trend. This trend will continue when every physician, every board of health, and every branch of organized medicine fully realize that the serious late complications of syphilis are the result of inadequately managed early syphilis.

Certain signs and symptoms have always received considerable attention from various authors. Moore, Danglede, and Reisinger<sup>5</sup> have recently tabulated the following criteria for the diagnosis of uncomplicated syphilitic aortitis: (1) teleroentgenographic and fluoroscopic evidence of aortic dilatation; (2) a tympanitic, bell-like, tambour accentuation of the aortic second sound; (3) a history of circulatory embarrassment; (4) in-

2. The various types of complications are given and their effect on the course of the disease emphasized.

3. The indications for and the results of medical and surgical treatment are summarized.

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often repeated is that every adult syphilitic patient must be considered as a probable victim of syphilitic aortitis, and the therapeutic approach, with a long follow-up period, must be carried out with that possibility always in mind.

#### THE AVERAGE LIFE HISTORY OF CASES OF SYPHILITIC AORTIC INSUFFICIENCY AS OBSERVED IN THE WARDS OF A LARGE CHARITY HOSPITAL

In an attempt to reconstruct the average picture of what occurs in uncomplicated syphilitic aortic insufficiency when it is the only cause of death, certain factors have been assembled in a group of 41 cases observed at autopsy, but not studied clinically. This is of some interest since, at the autopsy table, we often see syphilis of the aorta complicated by pathologic changes in many other organs, and it is not always clear what part syphilis has played in the termination of the case. In this group the average age was 42.1 years, the youngest case was 25 years of age and the oldest 65 years. There were six cases under 30 years of age, 15 in the fourth decade, and 14 in the fifth decade. The remaining six were between 51 and 65 years of age. Thirty belonged to the colored race, and eleven were white. Twenty-seven were males and 14 females. The average duration of symptoms before hospital aid was sought was 6.2 months, the shortest duration three weeks, and the longest two years. The average period in the hospital before death occurred was four weeks, giving an actual duration of the illness in this group of 41 cases of seven months. This is the course often observed in patients on our charity wards, but would not be true of a larger, more intelligent group upon whom treatment had been wisely instituted at an earlier period. Certainly, treatment as outlined by the Co-operative Clinic Group,<sup>10</sup> when instituted even in the stage of well-developed aortic incompetency, is often capable of prolonging life for from two to four years. However, this short survival period in our cases emphasizes the malignancy of this process after symptoms have developed.

In 26 cases of this group the chief presenting symptom was dyspnea on exertion, later followed by cough and ankle edema. In eight cases the presenting symptom was paroxysmal pain, present in three at rest, and in one radiating to the left arm. In the other five pain developed only upon exertion. The pain was always described as beneath the upper sternum and appeared not to differ from the types of pain occurring with disease of the coronary arteries. The pathology of these eight cases is of some interest. All revealed valvular deformity, but in three the left coronary ostium was entirely closed, in four the right coronary ostium was tightly sealed, and in the remaining case both coronary ostia were reduced to barely visible openings. Anoxemia of the heart muscle must have been a marked factor in the production of pain. The total duration of symptoms in these eight cases was no longer than for the group which showed no coronary involvement. The shortest duration in any case was six weeks, in which the

vive over long periods of years in the human body without producing demonstrable physical signs or clearly-defined subjective symptoms.

#### CLINICAL PATHOLOGICAL ANATOMY OF SYPHILITIC AORTITIS AS IT INVOLVES THE PROXIMAL AND ASCENDING AORTA

*Figure A:* Note that the superior vena cava (s.v.c.) and the inferior vena cava (i.v.c.) are located on a plane posterior to that of the aorta. The pulmonary artery (PA) is often on a slightly anterior plane to that of the aorta. Note the planes of the aortic and pulmonary valves (dotted lines) and that, on the anterior facies, the first 1.5 to 2 cm. of the ascending aorta is overlaid by the right auricular appendage (R.A.A.). This factor is of considerable importance, since in the great majority of cases syphilis begins in the first few centimeters of the aorta, and this portion, unless dilatation is extreme, cannot be easily visualized even by the Roentgen method, since it is located deep in the base of the heart. The numerals indicate the average transverse diameter of the portions of the heart which present themselves on the anterior facies.

*Figure B:* Depicts the normal aortic ring laid open with the proximal portion of the ascending aorta. It is convenient to classify lesions according to anatomical locations, as follows:

*Sinus Aorta:* The aorta just above the aortic ring and behind the aortic leaflets. A lesion here is not common and, if it occurs, may be manifested by bulgings and pulsations at the base of the heart, as shown, sinus of Valsalva (S.V.), figure A. Here are found rare sinus of Valsalva aneurysms and still rarer gummatous lesions. Roentgenologically, these bulgings produce most confusing pictures at the base of the heart.

*Commissural Aorta:* The angle formed by the meeting of two adjacent leaflets. Syphilis in this situation may extend to the neighboring leaflets, with resultant valvulitis. Syphilis is never primary in the valve leaflets, but always follows syphilis of the commissural aorta by extension. Very rare exceptions to this have been noted. A typical lesion is an elevation of the commissure with thickening of the commissural aorta, which is intermingled frequently in an atheromatous infiltration (the aorta here may be 3 to 12 mm. in thickness). In figure D, d'' is a syphilitic commissural infiltration and a dotted line connects it with a vertical section through its middle, showing the markedly infiltrated commissural aorta (D, d'',s).

The effects on the aortic leaflets may be at one or more commissures, as follows:

Commissural infiltration and elevation without valve separation: diastolic incompetency would develop only in the presence of greatly increased diastolic pressure (figure D, d).

Commissural infiltration and elevation with valve separation: see figure D, commissure d''; the interval between the adjacent valve leaflets may be as much as 5 to 12 mm. Marked diastolic incompetency develops.

*Marginal Valve Thickening:* In this type, which is uncommon, the free valve margin is invaded from the commissure. It becomes thickened and rolled up, as it were, and its extremities at the commissural regions become adherent to the adjacent aorta. The valve is decreased in depth and width; it is tense and often closely apposed to the aorta. Its normal valvular function is very much impaired, and the diastolic incompetency marked. See figure D, d', with vertical section d' of margin of valve, showing marked thickening of lunular portion of the valve, which is normally of tissue paper thickness.

*Hinge Valve Deformity:* A transverse thickened band develops across the middle of the valve, producing transverse shortening with the free upper portion moving to



dial pain or paroxysmal dyspnea in patients having a positive blood Wassermann reaction. In a few cases the diagnosis was made in the absence of a positive serology when the history and the clinical findings seemed sufficient evidence of the disease. The second criterion adopted, namely, persistent systolic murmur over the aortic area in the presence of a positive serology, was found to be of little or no value. Whereas a loud systolic aortic murmur is often heard in dilated syphilitic aortas, it is also heard when the aorta is dilated from other causes or when it is displaced, kinked, or the seat of rheumatic or sclerotic changes. Of the 70 cases, 60 are males and 10 females, an incidence of six to one, giving the males slightly over 85 per cent of the total, while the average from many observers would appear to be about 75 per cent. Fifty-three of the patients here reported are of the colored race and 17 of the white; but this incidence of white to colored is not entirely typical, since the cases are taken from the wards of the largest charity hospital in the city, where a large negro population is served. The racial percentage will naturally vary with the material studied, and in many series the percentage of negroes has been found as low as 23 per cent. In Scott's series<sup>3</sup> the proportion between white and colored was 34 to 41. Paullin<sup>12</sup> stated that 40 per cent of the negroes with syphilis show cardiovascular involvement. The percentage in the white race may be as high. It is evident that figures from different localities will vary with the proportion of negroes in the population.

*Age Incidence:* The following table gives the relation of cardiovascular syphilis to age:

Ages	Number of Cases	Per cent
20-30 .....	4	5.7
31-40 .....	11	15.9
41-50 .....	30	42.8
51-60 .....	23	32.8
61- .....	2	2.8
	<hr/> 70	<hr/> 100.0

The greatest number of cases, 75 per cent, falls in the fifth and sixth decades, the largest single group being 42.8 per cent in the fifth decade. The average age is 46.04 years. Thus the great majority of cases occur in midlife, falling between two other great etiological factors in heart disease, rheumatic affections and atheromatous changes. The youngest case in this series is 28 years; the oldest, 64 years.

#### THE LATENT PERIOD BETWEEN SYPHILITIC INFECTION AND ONSET OF SYMPTOMS

There is a long latent period, which may vary from five to 40 years, between the initial infection and the onset of symptoms. This information was available in 34 of the cases in this series. The shortest lapse of time between the initial lesion and the development of symptoms was five years; in two cases it was six years; and in one case, seven years. The

and fro in the blood stream. This produces a loud diastolic musical murmur and a thrill. Figure D,  $d'''$  and vertical section through  $d'''$ , 3 is the free portion of the hinged valve.

*Suprasinus Aorta:* The right and left coronary ostia are found here: The fibrosis of syphilis may produce orificial stenosis or atresia, with resulting ischemia of the myocardium (see figure D,  $d^2$ ).

*Ascending Aorta:* For clinical purposes, syphilis here may be classified as follows:

Extent of the syphilitic process

Discrete: A single lesion with a wide surrounding area of non-syphilitic aorta (figure C, 1).

Disseminated: Numerous individual syphilitic lesions with non-syphilitic aorta between (figure C, 2).

Diffuse: Syphilis of a segment of the aorta with no intervening non-syphilitic portion (figure C, 3).

Thickness of the diseased aorta:

Atrophic type, less than normal (figure C, 5).

Medium type, normal thickness,  $1\frac{1}{2}$  mm. (figure C, 4).

Productive or hyperplastic type, 2 to 6 mm. in thickness (figure C, 6).

Based upon these pathological criteria, syphilitic aortitis presents itself as:

*Saccular dilatation* (figure C<sup>s</sup>), and saccular aneurysm, figure C<sup>s'</sup>, in which rupture has occurred through the media of C<sup>s</sup>. Although there is considerable confusion in the terminology of aneurysm, my feeling is that as long as the media and intima are intact the term dilatation should be used, in that the lesion is relatively benign at this time. When rupture has occurred through these two layers of the aorta the lesion becomes malignant and then only should be dignified by the name aneurysm. These lesions are usually produced by a combination of discrete C<sup>1</sup> and atrophic C<sup>5</sup> syphilis.

*Fusiform Dilatation* (figure C<sup>f</sup>): Usually a combination of atrophic C<sup>5</sup> and diffuse C<sup>3</sup> syphilis. Such dilatations are usually found in the atrophic type, are often benign, have in the past been frequently wired, and often produce no symptoms. They may be found at autopsy even in the seventh and eighth decades of life. The diameter of the dilatation may be 8 to 12 centimeters.

Medium type: This is generally of the diffuse class, C<sup>3</sup>. The combination of medium type syphilis with either discrete or disseminated lesions often results in an aorta of normal thickness, normal diameter, and often of considerable elasticity (figure C<sup>s2</sup>).

Diffuse hyperplastic type: This is usually a combination of types C<sup>3</sup> and C<sup>6</sup>. The aorta is inelastic, but often of normal diameter.

Syphilis and atheroma, disseminated: This may be found in association with any of the preceding classifications (figure C<sup>e</sup>).

These are the types of syphilitic aortitis often seen at the autopsy table, and various complicated combinations are frequently in evidence.

Involvement of the myocardium occurs in syphilis, but is infrequent. Paullin<sup>2</sup> has recently described the various myocardial types of lesions.

### UNCOMPLICATED SYPHILITIC AORTITIS

My interest in the study of syphilitic aortitis was greatly stimulated by Scott's most excellent presentation.<sup>3</sup> He stated:

Practically all the cases of this series were studied at some time with the fluoroscope, and many teleroentgenograms were made. Definite cardiac enlargement was present in 93 per cent of the group. In those cases in which dilatation had not occurred the silhouette was the one often associated with aortic reflux, i.e., elongation downward and outward of the left ventricular curve. When dilatation is added this silhouette disappears, and we find diffuse enlargement to both right and left, with hazy borders, and the apex often reaching to the left costal border.

*Murmurs and Thrills:* The characteristic murmur of aortic insufficiency is usually of the typical to-and-fro quality often heard all over the precordium, but at times localized in the third or fourth intercostal space near the sternum on the left side, and we have observed many cases where it is best heard near or at the apex. When only the posterior cusp of the aortic valve is involved it may be best heard on the right side and may be transmitted downward toward the liver. In this series, the typical to-and-fro murmur was identified at some time during the observation in 61 cases (87 per cent). In the remaining nine cases a diastolic murmur was heard in each case at some time during the study. Occasionally one heard a rumbling presystolic murmur at the apex; and this represents a Flint murmur, since the results of many autopsies have shown that syphilis does not attack the mitral valve. A Flint rumble was thought to be present in only a few cases and then was a transient finding. A true Flint murmur is a "blubbery presystolic murmur," identical with that heard in mitral stenosis. It is never a "rumbling diastolic murmur" or a "long diastolic murmur," but constantly maintains its presystolic quality and ends with a sharp first sound. This murmur has been described as being present in 50 per cent of cases of uncomplicated aortic insufficiency, but is often transient and will be found in direct proportion to the diligence with which it is sought. The diastolic murmur of aortic insufficiency is often heard best at the apex or beyond, and its characteristic qualities may then be altered, but careful timing will often prove it to be a propagated aortic murmur. These factors might account for the large number of Flint murmurs heard, but in our experience a Flint murmur has proved to be difficult to identify and of doubtful value in differential diagnosis. A systolic thrill was felt over the base of the heart, most often in the right second intercostal space, in 18 cases (25.7 per cent).

In five cases a peculiar musical diastolic murmur was heard, which seems worthy of comment. Musical murmurs are usually heard over the base of the heart in the aortic area. They are most often diastolic, rarely systolic, in time. The usual explanation given for such musical diastolic murmurs is a rupture of a valve segment, perforation of a valve segment, or a cord-like strand of tissue across the valve orifice. These five cases showed all the signs of aortic incompetence, in addition to this unusually loud high-pitched musical diastolic murmur. Its very loudness suggested something moving freely back and forth in the blood stream. The murmur was variable in

creased retromanubrial dullness; (5) progressive cardiac failure; (6) substernal pain; (7) paroxysmal dyspnea. These diagnostic criteria have been adopted by the Coöperative Clinical Group<sup>10</sup> engaged in the study of the treatment of syphilis. That syphilis of the aorta can produce the above physical signs is readily admitted. The characteristic symptoms, so-called, of uncomplicated syphilitic aortitis, however, are by no means indisputable. It has been the experience of the author that such characteristic symptoms seldom occur in pure uncomplicated aortitis, and when they do occur one invariably finds evidence of aortic insufficiency, aneurysm, hypertensive disease, or myocarditis. Wilson,<sup>6</sup> from a recent analysis, has reached the conclusion that uncomplicated syphilitic aortitis is an asymptomatic condition, for in every instance where cardiac or respiratory symptoms occurred they were shown to be due to some factor other than the simple aortic disease, usually an extension or complication of the syphilitic process, or some unrelated condition.

Very favorable results of the early diagnosis of uncomplicated syphilitic aortitis have been reported by various students of the problem; namely, Maynard and his associates,<sup>7</sup> Steel,<sup>8</sup> Sproull,<sup>9</sup> and others. They have found the roentgen method of examination of the aorta of great value in the early detection of disease and determination of its extent. We have recognized that there are serious stumbling blocks in diagnosing syphilitic involvement of the aorta in early cases of syphilis: first, because the aorta is anatomically deep-seated; and, second, because we must exclude changes that come from other conditions, e.g., the tortuous, kinked, often dilated and elongated arteriosclerotic aorta found in the middle-age group; the changes that come from hypertension, from decreased spatial relations of the thoracic cage, and from the early aging process in the laboring classes. We have concluded that a positive diagnosis may be established when a saccular aneurysm is present, when aortic regurgitation appears for the first time in an individual of the middle-age group with a positive serology, or when a diffusely dilated aorta is found without aortic regurgitation and in the absence of hypertension or a history of such. The fact that the syphilitic aorta is often of normal diameter and normal thickness adds to the diagnostic difficulty. Our studies lead us to the conclusion that the early diagnosis of uncomplicated aortic syphilis is practically impossible except by inference.

It is apparent, then, that atheroma and dilatation of the aorta with or without hypertension often offer serious differential diagnostic difficulties, and that in the absence of a definite history, positive blood reaction, or other aids, the diagnosis of uncomplicated syphilitic aortitis will seldom be safely established before the advent of complicating pathology. In the last analysis, the attempt to diagnose uncomplicated syphilitic aortitis before it has produced structural or anatomical defects is not the most important factor. The one factor which needs constant emphasis and cannot be too

thought to be present in possibly 35 cases of the group (50 per cent). This same type of ringing, metallic aortic second sound is heard so often in other conditions, such as hypertension and arteriosclerosis, that in our judgment its presence is of little or no diagnostic value. The aortic second sound was entirely absent in only 15 cases (20 per cent). It is interesting to note that the aortic second sound may remain intact for a long time in syphilitic aortic insufficiency, in contradistinction to rheumatic aortic disease, where in advanced cases the second sound is often absent.

*The Roentgenogram and Fluoroscope in Syphilitic Aortitis:* Kurtz and Eyster<sup>14</sup> have made excellent studies of the configuration of the normal as well as of the syphilitic aorta. Since their deductions are largely in keeping with my own observations, they might be briefly summarized as follows: The configuration of the aorta is influenced by many factors. Among these, importance should be given to the increased and decreased spatial relations of the thoracic cage. When the diaphragm is high (as in sthenic types, abdominal tumors, ascites, and even expiration), the aorta spreads out, increases in height and becomes more prominent to both the right and left. With a low diaphragm, the vascular shadow is narrower. The ascending aorta can usually be seen in all views before the age of 50. It is behind and directly to the left of the sternum at the level of the first to the third ribs. Elongation of the aorta begins early in life, especially in the laboring classes, even in the absence of hypertension. When elongation takes place, the aorta increases in density, appears to sag somewhat, and the pulsations are more prominent to the right of the sternum. In the forties and especially after 50 years of age, the increased density of the aorta makes the thoracic portion clearly visible, while its tortuosity may become extreme. When these changes are observed in a person in the thirties or early forties, it would be natural to assume some degenerative process. Hypertension, age, atherosclerosis, rheumatic aortic insufficiency and stenosis of the isthmus all cause changes in the aorta which may be confused with and so must be differentiated from syphilis. Several excellent studies of aortic changes induced by syphilis from both roentgenographic and fluoroscopic aspects have been made by various students of the subject, namely, A. O. Hampton, et al.,<sup>15</sup> and P. V. Ledbetter, et al.<sup>16</sup> Since no recent, new or valuable signs have been reported, the following deductions may be of considerable aid when conservatively applied. The changes which may be suggestive of syphilis are dense shadows with hazy borders; the presence of a high, prominent, dense aortic knob, which is also hazy; irregular and diffuse dilatation with no clearly-defined borders; increased pulsations, associated with the silhouette of aortic insufficiency; angulation at the junction of the ascending and transverse portions of the aorta, best seen on the lateral view with the fluoroscope. These changes are not characteristic of syphilis, and the fluoroscope alone should not be used for diagnosis. Lack of appreciation of this fact leads to constant mistakes. If the fluoroscopic findings are sug-

coronary ostia were free, but the aorta revealed a diffuse aortitis with valve distortions. The entire group was diagnosed while under observation as aortic incompetency and myocardial failure of the congestive type. The Wassermann reaction, taken in 35 of the cases, was reported positive in 34 (83 per cent) and negative in one. All cases were reported to have a collapsing type of pulse, and the average pulse pressure was 89 mm. The highest systolic pressure reported was 180 mm. The average diastolic pressure was 55 mm. A syphilitic involvement of the aortic valve area was found in all and varied from widening of the commissures, with intimal proliferation at the commissural junction, to thickening and fibrosis of the valve leaflets with shortening and retraction.

In 22 cases diffuse aortitis involving the ascending and transverse arch was present. In the remaining 19 cases the process was confined to the aortic valve area and the first two inches of the aorta. No case was observed in which the syphilitic process was confined to the valve area alone. This bears out the well-known fact that syphilis practically always starts as a simple aortitis in the suprasinus portion of the aorta and involves the commissures and aortic leaflets by extension through the vasa vasorum. The average measurement of the aortic ring was 7.3 cm., the largest 7.8 cm. This is of importance, since many believe that dilatation of the aortic ring is a factor in syphilitic aortic insufficiency, which has not been my experience. The condition where dilatation of the ring plays a part in the insufficiency is by involvement of the aorta just above the ring in an aneurysmal dilatation, which at times may be sufficient to distort the fibrous ring without its actual involvement in the process. These are sinus of Valsalva aneurysms<sup>11</sup> and may produce aneurysm and cardiac hypertrophy without syphilis of the aortic valve. These sinus aneurysms often produce very complicated lesions about the root of the aorta, both clinically and pathologically. One case which had been diagnosed as aortic insufficiency with aneurysm of the ascending aorta proved, at autopsy, to be due to a transverse tear through a syphilitic process just above the valve area producing a dissecting type of aneurysm, the aortic valve area, however, being uninvolved. Ruptures of the aortic wall are distinctly uncommon in syphilis, the great majority occurring in hypertensive disease. The average weight of the hearts in this series proved to be 585 grams, the average weight in males being 640 grams and in females 530 grams.

#### SYPHILIS OF THE AORTIC VALVE AREA

The material for this discussion includes 70 cases of active syphilitic aortic insufficiency admitted to our medical service. Every effort was made to exclude doubtful cases, the criteria for diagnosis being: (1) aortic regurgitation in patients with a positive blood Wassermann reaction; (2) persistent systolic murmur over the aortic area in the presence of a positive blood Wassermann reaction; (3) symptomatic evidence of heart failure, precor-

majority of cases is caused by syphilis, rheumatism, or atherosclerosis. Considerable difficulty is often encountered in determining etiologically the type of insufficiency present. The most reliable statistics would indicate that syphilis is the cause in 75 per cent of the cases and that aortic reflux develops at some time in the course of 70 per cent of the cases of aortitis. Rheumatic heart disease probably offers the greatest difficulty in differential diagnosis, but the rheumatic heart practically always comes to the observation of the clinician before the age of 30. Rheumatic heart disease is a disease of young people, and the great majority are dead at 40. A history of rheumatism is often obtained, and only a few cases of rheumatic heart disease make their first appearance in the third or fourth decade. Syphilis of the aorta, on the contrary, usually first manifests itself as a disease of mid-life, a few cases beginning in the third decade, but by far the great majority coming between the age periods of 35 to 55. It is, therefore, usually too late to be the first manifestation of rheumatism and too early to be a purely atheromatous process. Given a definite history of rheumatism, with no evidence of syphilis, combined with a mitral lesion, and the problem offers no special difficulties. In cases with no history or evidence of syphilis or rheumatic fever, as well as those with a history of both syphilis and rheumatic fever, we should remember that the aortic insufficiency of syphilis exceeds all other types combined and may be due to syphilis when all other indications of the disease are lacking. The patient with syphilis of his aortic valves has a poor prognosis and lives but a short time after coming under observation, whereas the rheumatic aortic insufficiency often has a good prognosis and lives a longer time. Rheumatism and syphilis almost never affect the same heart, and certainly a combination of hypertensive disease with either of these infections is not common. The importance of this fact is that, if we have satisfactorily identified syphilitic aortic valve disease, we can be practically certain that the other is absent and the other valves sound. Likewise, if we can satisfactorily establish the diagnosis of rheumatic mitral disease, we can be practically certain that what we hear at the aortic valve area is rheumatic disease also. In syphilis of the aortic valve area, the visible signs of suprasternal pulsations, dancing carotids and brachials, are usually present, but may not be so prominent as in rheumatic disease, since in syphilitic aortitis there may be interposed between the insufficient aortic valves and peripheral vessels a relatively long stretch of inelastic and diseased aorta. To these statements there are many exceptions, because numerous individuals with uncomplicated rheumatic aortic insufficiency live out the normal span of life. It is often a peculiarly benign lesion, and in some sections of the country rheumatic aortic insufficiency is commoner than the syphilitic form. Uncomplicated rheumatic aortic insufficiency often produces no symptoms for years, and thus these cases do not reach our hospital wards or even the outpatient department. Statistics gathered from hospital admissions may have in

longest latent period between the infection and the onset of symptoms was 34 years; the average interval was 22 years. In Scott's series<sup>9</sup> the average latent period was 20 years; the longest, 44 years. Longcope<sup>13</sup> reported 19 cases between the ages of 20 and 30 years, and gave the average latent period in his 63 cases as 16 years. Syphilitic infection of the aorta may be found at autopsy during the secondary stage.

*Presenting Symptoms:* By this we imply the patient's most troublesome complaint, or the subjective feelings which caused him to seek medical attention. In the past, many authors have placed undue significance on two presenting symptoms, namely, paroxysmal dyspnea and substernal pain or oppression, and we have attempted to determine the incidence of these as presenting symptoms. In only six cases was paroxysmal dyspnea a factor in the onset. In 12 cases pain was a part of the initial complaint, but was not emphasized in the history, as it was always accompanied by other symptoms to which the patient gave more significance. The most frequent early symptom was dyspnea on exertion, and this was present in 50 patients (71 per cent). There were other minor complaints, such as a feeling of fluttering in the chest, nervousness and cough. It will be seen then that by far the greater number had as the presenting symptom dyspnea on exertion, often accompanied by a mild degree of pain. There were no cases in this group which could be classified as having pain of the angina pectoris type. The question of the incidence of paroxysmal dyspnea is hard to determine, since it is our belief that it varies with the social status of the individual. Longcope<sup>13</sup> found it in 14 per cent of his patients. It is nearly always associated with marked cardiac enlargement. In 12 patients pain was a moderate factor in the initial symptoms, was usually substernal, and did not radiate. In 20 other patients, tightness or oppression under the sternum was emphasized, which in a more sensitive group would, no doubt, be classed as pain. Longcope<sup>13</sup> states that 46 per cent of the cases in his series gave a definite history of pain. Although pain may be one of the most characteristic symptoms of syphilitic aortitis, its importance in diagnosis should not receive over-emphasis, since it may be absent in more than half of the cases. The average duration of symptoms before the patient was forced to seek hospital attention was, in this group, 10 months, the longest duration being five years and the shortest, two weeks. In 40 per cent, edema of the ankles was present upon first admission to the hospital.

*Cardiac Enlargement:* The cardiac enlargement in aortic valvular disease will naturally vary with the extent and the duration of the condition. With involvement of only one cusp the leakage is moderate, whereas in others it seems to be extreme. Physiologists have determined that from 8 to 58 per cent of the blood ejected at each systole may regurgitate into the ventricle in insufficiency of the aortic valve. Such a reflux naturally leads to hypertrophy. Add to this the dilatation which accompanies myocardial breakdown, and the enlargement on physical examination may be extreme.



and inelastic tube, it destroys the integrity of the semilunar valves, and often narrows the coronary mouths. It is small wonder then, that once the syphilitic process has reached a certain stage and this mechanism has been destroyed, the heart muscle rapidly disintegrates.

### SUMMARY

A detailed study of 70 cases of syphilitic aortic insufficiency forms the basis of this report. In addition, the pathology of syphilitic aortitis, the diagnosis of uncomplicated syphilitic aortitis and an analysis of 41 cases of syphilitic aortic incompetency which came to autopsy have been presented. Of the 70 cases in the series the ratio of males to females was six to one. Fifty-three of the patients were colored; 17 were white. The average age was 46.04, with extremes between 28 and 64. The average interval between primary infection and the onset of symptoms was 22 years. The most common presenting symptom was dyspnea on exertion, which occurred in 71 per cent. The rarity of paroxysmal dyspnea and pain was noted. An increase in the size of the heart was noted in 93 per cent. The average duration of symptoms before medical attention was sought was 10 months, the shortest two weeks, and the longest five years. Edema of the ankles was present in 40 per cent upon first admission to the hospital. The typical to-and-fro murmur of aortic insufficiency was present in 87 per cent. The presence of a loud musical diastolic murmur and thrill in five patients was discussed and its pathology explained. The average pulse pressure was 84 mm. of mercury. The Wassermann reaction was positive in 85 per cent of the patients. In addition, the appearance on fluoroscopic examination was discussed, and the absence of any noteworthy features in the electrocardiogram stressed. The differential diagnosis between syphilis, rheumatism, hypertension, and atheroma of the aortic valve was considered. The salient points in the clinical course of the disease were discussed, and a possible explanation suggested for the rapid myocardial breakdown.

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intensity and exaggerated by exercise. It was loudest over the aorta, but widely transmitted over the chest and, in three cases, was heard distinctly in the back. It was distinctly decrescendo in type and usually filled the entire diastole. In each case the patient was conscious of this "whizzing" or "singing" noise in his chest, and in three of the cases it was sufficiently loud to be audible to the unaided ear of the examiner at a distance of from one to three feet from the chest wall. It was in all cases accompanied by a thrill, diastolic in time, most marked over the upper sternum and transmitted widely to the whole chest wall, but not to the soft structures of the neck. That this murmur developed its intensity rather suddenly is attested by the fact that in three cases it occurred after a hard day's work and, in at least two and probably three cases, marked the beginning of myocardial failure.

Three of these cases came to autopsy. The findings in two were eversion or fracture of the upper part of the right anterior aortic leaflet. The widening of the commissures and the fibrotic process which may follow in the aortic leaflet tend to narrow the leaflet longitudinally; the upper half becomes very thick and thus is in a position to evert itself upon the more delicate valve portion beneath it, which has not shared so profusely in the process. This is the typical hinged-valve deformity.

The audibility of this sound to the patient has been explained because the anterior aortic leaflet lies nearest the sternum, and thus bone conduction is brought into play. This, however, cannot be the only explanation, as, in one of these autopsy cases in which the patient had been conscious of the murmur, the posterior cusp of the aortic valve was shortened and drawn tightly against the intima of the aorta, so that it could function as a cord-like strand of tissue across the valve orifice and vibrate in the regurgitant diastolic current of blood.

*Pulse and Blood Pressure:* The Corrigan or water-hammer pulse is always emphasized in the diagnosis of aortic insufficiency. It was definitely present in 56 cases of this group (80 per cent). The highest pressure noted was 205 systolic and 50 diastolic, this case presenting both a Corrigan pulse and a double aortic murmur. The lowest blood pressure recorded was 90 systolic and 40 diastolic, and here also a Corrigan pulse and a to-and-fro aortic murmur were present. The average pulse pressure in this series was 84 mm. of mercury, which bears out the clinical fact that a collapsing pulse is frequently associated with a high pulse pressure. In a study of the blood pressure range in this group of aortic insufficiency it becomes evident that a diagnosis of hypertension in the presence of aortic reflux should not be made unless the systolic pressure is above 200 mm. of mercury.

*Aortic Second Sound:* The peculiar hollow, amphoric aortic second sound has been described as characteristic of syphilis. Its peculiarity has been explained from the fact that it is made in a dilated aorta, the walls of which have undergone little or no calcification. It is thus considered unlike that heard in atheroma and hypertension. This "bruit de tabourka" was

# CHRONIC DISSECTING ANEURYSM OF THE AORTA, SIMULATING SYPHILITIC CARDIOVASCULAR DISEASE; NOTES ON THE ASSOCIATED AORTIC MURMURS \*

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IN the last 10 years, 31 cases of dissecting aneurysm of the aorta have been observed at necropsy at the Philadelphia General Hospital, an incidence of 1:480 in necropsies of patients over the age of 20 years.† Sixteen of these cases had presented the characteristic feature of dissection of the aorta, namely, the abrupt onset of severe and often excruciating pain which was usually thoracic, but also frequently abdominal, occurring in hypertensive patients and followed in most instances by sudden death. The duration of life from the onset of pain was short, generally a matter of hours or of a few days. It was prolonged in some cases for six or seven weeks, but even in these instances, despite the complete cessation of pain, death was characteristically sudden.

The remaining cases were atypical. Hypertension or a previous history of it was present in every case, but pain was variable in extent and intensity. In some cases there was no pain; instead, syncope was the first and outstanding symptom. Such atypical cases are reported with increasing frequency, especially those which simulate chronic coronary disease and cerebral "accidents."<sup>1, 2</sup>

This report is concerned with six patients whose clinical course differed greatly from that commonly observed. They ranged in age as follows: 32, 44, 47, 50, 68, 69 years. There were four males, two females; all were negroes. Pain was absent in the history of four of these patients. It was inconspicuous in a fifth patient who was under close medical observation for almost four years (case 1, G. M.). This patient had at first some abdominal distress, but it was never severe, nor was it sufficiently localized to be of any diagnostic value. It disappeared long before death. Finally in the sixth case, precordial pain was complained of intermittently three weeks before death. The underlying pathologic changes were almost certainly present for at least many months before the onset of pain which apparently accompanied a terminal phase of the patient's illness.

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† This age selection was followed inasmuch as dissecting aortic aneurysm is rare in childhood and adolescence. Those cases of arteriosclerotic aneurysm, usually abdominal, which were complicated by small dissections of the adjacent vessel wall were excluded. Such minute dissections are usually the result of "medionecrosis aortae cystica," yet probably would not have occurred in the absence of the major arteriosclerotic factor. We included the occasional case where secondary dissection was prominent, i.e., 4 cm. or more.

gestive and can be correlated with a corroborative history, serological and physical findings, then and only then should the diagnosis be made. A generalized dilatation under the age of 45 will then be very significant. Arteriosclerosis of the aorta usually shows a prominent and sharply-defined aortic knob, in which calcified areas may be seen, whereas syphilis in contrast gives a blunting and dilatation at the root and ascending portions, with a hazy outline. Arteriosclerosis is best seen after 60, whereas syphilis is found much earlier. In hypertension the aorta often shows a marked degree of dilatation, but does not give the flat, flabby aorta of syphilis. The heart in hypertension is elongated and widened in about equal proportions; whereas in syphilis, before dilatation has become a factor, one sees marked lengthening, especially in the presence of aortic insufficiency. After heart failure occurs, the fluoroscopic differentiation between hypertension and aortic incompetency has in my experience been impossible. In rheumatic aortic insufficiency one sees a dilated ascending aorta, somewhat elongated, with increased pulsations, but the pulsations are usually more prominent than in syphilis and the dilatation more sharply localized to the right of the sternum. The rheumatic aorta is purely a mechanical phenomenon and, because of the absence of disease in its wall, is sharply outlined. Syphilis never produces narrowing in any portion of the aorta. Although it may appear easy to classify differential fluoroscopic findings in aortic syphilis, the results of many autopsies have proved to us that to all rules there must be many exceptions.

*The Wassermann Reaction:* The complement fixation test was positive in 60, or 85 per cent, of this series; negative in six; not noted in four. Two of the negative cases came to autopsy and were found to be syphilitic. This reaction, then, plays a dominant rôle in diagnosis and treatment, since the percentage of positive results has been established at a high level. In the statistics of other authors the average positive reactions in large series of cases have been 80 per cent. Naturally, syphilis of the heart and aorta may be present long after immune bodies have disappeared from the blood. If the clinical picture warrants the diagnosis, it can be safely made in the absence of a positive serological test, since the latter may be negative in as high as 20 per cent.

*The Electrocardiogram:* All cases in this series had one or more electrocardiograms. The most constant finding was a left axis deviation, which occurred in 50 cases (70 per cent). In addition, right bundle branch block was noted once, auricular tachycardia once, bigeminal rhythm once, and auricular fibrillation twice. The rarity of auricular fibrillation, even in cases with advanced myocardial failure, is especially worthy of note. Low voltage, notching, and slight widening of the complexes were not uncommon, but they are variations seen in any group of cardiac patients and were as valuable here as elsewhere in influencing prognosis.

*Differential Diagnosis:* Insufficiency of the aortic valve in the great

extending into the thoracic portion of the vessel. In all six cases the new channel began either at the aortic valvular orifice or from the root of the aorta immediately above the valvular ring.

The hearts were hypertrophied, their weight ranging from 420 to 900 grams. There were no abnormalities of the aortic commissures, but the aortic rings were dilated, markedly so in three instances. We noted also in each case a lipping or thickening of the central portions of the free margins of the aortic leaflets. The lateral portions of the leaflets adjacent to the commissures retained a normal delicacy. The central thickenings were evidently thickened *corpora aurantii*, the result, we think, of a constant "central" leakage through an aortic valve, the leaflets of which were no longer efficiently approximated in diastole. This type of "mechanical" aortic insufficiency which is seen in other types of cardiac disease will be described separately. The mitral valve was normal in every case.

The aortic dissection in all of these cases was apparently old, probably in some instances of many years' duration. It evidently recurred at various times, leading in two instances to a most intricate and extensive involvement. In one instance, the two "barrels" opened, side by side, directly into the left ventricle. The new channel evidently forced its way down into two sinuses of Valsalva, and then broke through internally at the aortic valvular orifice. Thus reëtrance was made in contact with the left ventricle, which literally now had two aortas. The new channel preëmpted most of the aortic valvular lumen and the original aorta was confined at its beginning to a small arc of its original lumen, i.e., comprising one aortic valvular sinus. The original aortic channel was identified by observing the origin of the carotid arteries.

The second instance of unusual aortic dissection showed a remarkable series of intercommunications and irregular projections (shelves, channels, telescopings). A detailed description of the case is beyond the scope of this report.

On gross examination, luetic aortitis was thought to be present in three cases, including the two mentioned above as having unusual dissections. This tentative diagnosis was reached because of the fine nodularity and scarring along the inner surface of the aorta. However, a review of our material shows that this suggestive scarring in case 1 (figure 1) is confined entirely to the new channel and almost entirely so confined in case 2 (figure 2). In another case, the irregular scarring was likewise found only in the new channel.

Histological examination of the aorta revealed the presence of Erdheim's "medionecrosis aortae cystica"<sup>3</sup> in four cases in which adequate sections had been preserved. There was no evidence of luetic aortitis in these cases (the one case with a positive Wassermann test was included). This conclusion was reached after studying numerous sections from different aortic levels. Sections from those areas in the new channels that grossly appeared

the past erroneously influenced our beliefs that syphilitic aortic insufficiency exceeds all other forms. It is probable that in the North and in the New England States the rheumatic type predominates.

*Clinical Course:* There are many factors in syphilis of the aorta which await elucidation. Among these may be mentioned the long latent period, the rapid progress when insufficiency becomes established, and the almost total lack of cardiac reserve shown by many of these cases. Ultimate myocardial failure awaits practically all cases of syphilitic aortic insufficiency, and the heart is totally unable to compensate for this lesion. Some patients are able to do light work for a few years, and the writer has under observation one case where disease has undoubtedly existed for seven years, but this is the rare exception and not the rule. An abrupt onset of symptoms with progressive cardiac failure is the typical picture, which is doubly discouraging since the condition is only slightly amenable to treatment at this stage and the progress is rapidly downward. Many such patients have been admitted repeatedly to our wards over a period of one or two years, and we have marveled at the almost insignificant reserve displayed by these hearts. The speed with which this type of heart failure progresses is singularly striking and is totally different from the types of failure observed in our wards in the hypertensive, rheumatic and coronary artery groups. Many patients coming under our observation do not recover from even their first attack of decompensation. Gross<sup>17</sup> recently stated that congestive heart failure is the failure of the heart which fails to undergo further hypertrophy, and that the cause may lie in some disturbance other than an anatomical one, although cardiac hypertrophy is the cardinal associated finding. He also discusses metabolic disturbances, which appear to be the ultimate cause of failure. These factors, as well as others, play a part in the failure of the hypertrophic heart of syphilitic aortic incompetency.

The flow of blood into the walls of the heart differs from that of any other organ, in that it must take place largely in diastole. When the heart is contracted its muscular walls are firm and hard, which naturally empties the veins but prevents filling of the coronary system. When the heart relaxes in diastole, blood from the aorta immediately above the semilunar valves can pass easily into the coronary arteries and forward into the rich capillary bed of the organ. The blood in the aorta during diastole is forced forward to the branches of the arterial tree by the elastic recoil of the thoracic aorta. This movement towards the periphery is made possible by closure of the aortic valves. There are three vital structures, therefore, concerned in the supply of blood to the heart: the aortic semilunar valves, the elastic aorta, and the coronary arteries; so that if the heart is to receive its normal blood supply, the aorta must be elastic, the semilunar valves intact, the coronary mouths open and their lumina distensible. It is obvious that the pathological process in syphilis of the root of the aorta disturbs this mechanism. It converts the aorta into a fibrous

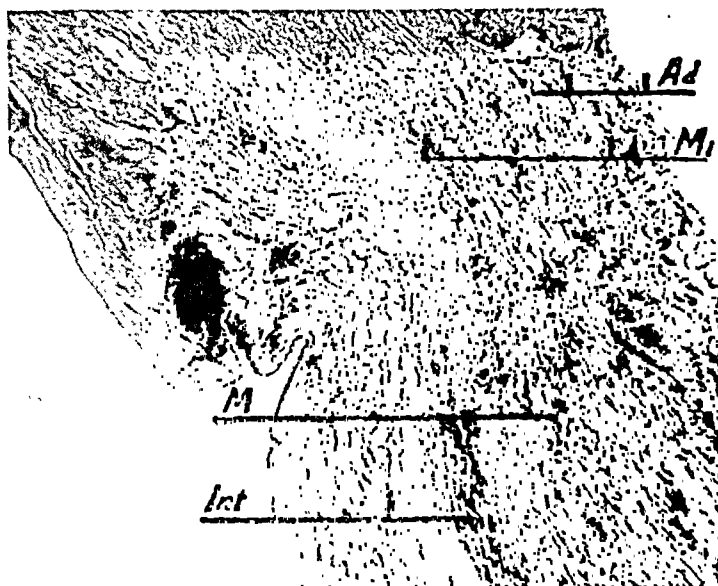


FIG. 2. Microscopic view, low power (Byer trichrome stain), of the dissected wall. There is a markedly thickened "intima" (Int) which in its deeper portion shows a zone of very compact, fibrous tissue. There is a prominent infolding of the new intimal structure not due to any contraction in the media. Note completely endothelialized surface. The media (M and M1) is irregularly narrow, less than  $\frac{1}{2}$  of its normal width and without any internal elastic membrane. The adventitia (Ad) is normal. High power examination revealed no cellular infiltration or scarring suggestive of syphilis.

than that seen in any aorta. This has been previously noted, but the peculiar roughening of the new surface seen in some of these cases may be emphasized, inasmuch as it appears to have been the reason in past years for a gross pathological diagnosis of syphilis which did not exist. Arteriolar sclerosis of the vasa vasorum was seen in two cases. It appeared here as part of a diffuse arteriolar sclerosis noted in the other tissues of the same patients.

Following are abstracts of the clinical-pathological findings in three cases.

#### CASE REPORTS

*Case 1.* G. M., a negro male, aged 41 years, became dyspneic in September 1935, and soon thereafter became aware of an intermittent pain or ache in the abdomen and xiphoid region. Increasing dyspnea and the appearance of bloody sputum led to hospitalization April 1, 1936. Luetic valvular heart disease and passive congestion of the liver were the major diagnoses, although it was noted that both the blood Wassermann and the Kahn tests were negative, as was also the spinal fluid Wassermann. Specific treatment was instituted, first with bismuth, later with neoarsphenamine. After temporarily good results, decompensation recurred and the patient was readmitted to the same hospital. The Wassermann reaction was again negative, but specific treatment was continued. Progressive leg edema and hemoptysis led to the patient's first admission to the Philadelphia General Hospital (November 18, 1936) on the service of Dr. David Riesman. The patient again spoke of a dull abdominal ache under the xiphoid and under the rib margins, intensified by eating and exertion. At this time, he was also aware of occasional numbness and tingling extending down both legs. These minor complaints were obscured by the cardiac decompensa-

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and thickness of speech. The patient stated that five years previously there had been an unexplained hemorrhage from the lungs. Examination showed a well nourished man with a stiffness and weakness of the left arm and leg. The deep reflexes in those extremities were exaggerated. Râles, apparently of congestive origin, were heard at the right lung base. The heart was markedly enlarged to the left, the apical beat being palpable in the anterior axillary line in the sixth interspace. A soft systolic murmur was heard there and there was also a soft systolic and a blowing diastolic murmur replacing the heart sounds in the aortic area. The blood pressure in both arms was 180/90. The area of supracardiac dullness was widened mostly to the right. Roentgen-ray examination (December 10, 1933) showed hypertrophy of the left ventricle and also marked widening of both the ascending and descending portions of the aorta. No definite evidence of aneurysm was noted but the roentgenologist made a diagnosis of luetic aortitis and aortic valvular insufficiency. The patient was discharged (January 1, 1934), but returned on August 11, 1934, on the neurological service of Dr. Bernard Alpers. He was dyspneic and dizziness recurred frequently. His blood pressure was now 210/90, there was a Corrigan pulse, and the diastolic aortic murmur was "loud, long, and blowing." No cyanosis or edema was noted, but the neck vessels were distended. Despite prolonged bed rest and digitalization, and the apparent improvement in strength in the left side extremities, dyspnea never entirely disappeared and from time to time became markedly aggravated. On November 18, 1936, the patient suddenly had several attacks of severe precordial pain, radiating down the left arm, all quickly relieved by nitroglycerine. Auricular fibrillation developed and dyspnea became increasingly severe. The pain disappeared about 10 days after its onset, but dyspnea continued. The patient died suddenly (December 15, 1936), presumably because of coronary artery occlusion. Kahn tests occasionally repeated during his two years of hospitalization had always been negative, as was the spinal Wassermann test. Nevertheless, the clear-cut picture of aortitis and aortic regurgitation was constantly present, the signs in fact becoming more pronounced with the passage of time.

Necropsy (Dr. Lannon) revealed an ancient dissecting aneurysm (double-barreled aorta) involving the entire length of the vessel.

## DISCUSSION

The interesting clinical aspect of these patients was the close resemblance borne to luetic heart disease, which deceived internists and cardiologists alike. Physical examination indicated the presence of aortitis and aortic valvular regurgitation, which, occurring in decompensating middle aged or elderly individuals, were reasonably assumed to be of syphilitic origin. In some instances anti-luetic treatment was instituted, timidly, of course, in view of the cardiac state. Case 1 (G. M.) received a more intensive type of therapy in another hospital consisting of repeated courses of bismuth and neoarsphenamine injections.

Cardiac murmurs indicative of aortic regurgitation have frequently been heard in patients with dissecting aneurysm of the aorta and instances of erroneous diagnosis of aortitis, saccular aneurysm and luetic aortic valvular insufficiency were noted many years ago by Letulle<sup>4</sup> and Boeger.<sup>5</sup> Most of the recorded instances, however, of such murmurs have been in patients with acute or relatively acute lesions, with typical clinical aspects and with only short periods of survival. Thus the problem of prolonged

All of these patients had cardiac decompensation, the duration of which varied from two months to four years. They all complained of shortness of breath and most of them had ankle edema and palpitation. Hemoptysis occurred possibly more often than is seen in even chronic decompensation. It was present in five of these patients, varying from ordinary blood spitting to frank hemorrhage, and in four instances it was noted in the early phase of the illness. In one instance (case 5, A. S.) hemoptysis preceded the appearance of decompensation. Despite hospital treatment, cardiac failure was progressive in each case and was eventually the cause of death. In case 5, it was complicated by paraplegia originating from the same pathologic change.

Examination revealed hypertension and enlargement of the heart, especially of the left ventricle. Murmurs were heard in both the mitral and aortic areas. The mitral murmurs present in four cases were soft, blowing and systolic; they were overshadowed by the aortic murmurs which were heard in every case. The latter were in the beginning usually "double murmurs," consisting of a short systolic murmur followed by a blowing diastolic murmur which was heard in both the second right intercostal space and down along the left sternal border. Eventually the systolic aortic murmur disappeared and the diastolic murmur became progressively more pronounced. In two instances, a diastolic aortic murmur was the only murmur heard throughout the period of observation. These murmurs led to the diagnosis of aortic regurgitation. A Corrigan pulse and a widened pulse pressure were present in every case. Inconstant findings were Austin Flint murmurs, apical gallop rhythm, Durozier's murmur, and capillary pulse.

The area of supracardiac dullness was widened and roentgen-ray evidence of a dilated aortic arch was recorded in every case. Aphonia occurred once, but a tracheal tug was not felt in any patient. Marked enlargement of the liver was noted in each case, hydrothorax twice. The Wassermann and Kahn tests were repeatedly negative in five of the six patients, and the spinal Wassermann tests in the blood negative cases were likewise all negative. A history, however, of a penile lesion, presumably syphilitic, occurring in youth, was obtained in two patients, one of whom had the positive Wassermann test. A diagnosis of chronic luetic cardiovascular disease with aortitis and aortic valvular regurgitation was made in every case.

#### PATHOLOGICAL CHANGES

Necropsy in these cases surprisingly revealed the presence of dissecting aneurysm of the aorta of the chronic type. The dissected areas were completely endothelialized. There were four instances of "double barrel" aorta, the new channel communicating with the original at both the most proximal and the most distal portions of the vessel. In the two remaining cases, dissection remained entirely intramural, confined within the media, but extending for a considerable distance, beginning at the root of the aorta and



FIG. 3. (Case 3.) Remarkable destruction of the aortic wall in chronic dissecting aneurysm. A horizontal ridge (A) above the aortic valvular ring marks the end of the original channel. Even below this ridge is an orifice leading to the false channel. The original intima and adjoining media have been rolled up into the upper portion of the aortic arch where they have been crumpled, invaginated, and distorted in a most irregular manner (B). Another dissection occurs further up (C). The surface of the dissected channel is irregularly scarred, suggestively like that in luetic aortas; there was no histologic evidence of syphilis. Note lipping and thickening of the central portions of the free margin of each aortic leaflet.

luetic, showed that the deceptive appearance was due to an irregular scarring and infolding of the new subendothelial fibro-elastic tissue, apparently a part of the endothelialization process. The new "intimal" layer is much thicker



FIG. 1. (Case 1, G. M.) Ancient dissecting aneurysm of the aorta, with two "aortas" emerging from the left ventricle. The original aorta (from which the innominate and carotid arteries arise) is marked by a glass rod. Its connection with the aortic valvular lumen is now limited to a small arc of that lumen, comprising scarcely more than one sinus of Valsalva. The wide expanse of aortic structure (in the ascending arch) is the secondary or dissected channel, free of thrombus and thoroughly endothelialized. It leads directly from the left ventricle, the dissection having forced its way down to that chamber long ago. Its fine irregular scarring strongly suggested luetic aortitis, which was not corroborated by microscopy (figure 2). Note marked enlargement of left ventricle and the lipping and thickening of the free margins of the aortic leaflets. The commissures are normal, the bodies of the aortic leaflets normally delicate.

tion, accompanied by increasing hemoptysis. Examination revealed a systolic blood pressure of 210 with a diastolic level of 105, a blowing diastolic aortic murmur, gallop rhythm at the apex and marked cardiac enlargement. Fluoroscopy also revealed dilatation of the root of the aorta. The liver was greatly enlarged and tender. Basal congestion of the lungs, pitting edema of the legs, and a mild degree of icterus also were noted. Venous hypertension and dyspnea were partially relieved by venesection. Further improvement followed digitalization and the patient was discharged December 14, 1936, to the heart clinic, only to be readmitted February 11, 1937, with recurring decompensation. The blood pressure was 210 systolic and 80 diastolic and the peripheral signs of aortic regurgitation were pronounced. A short low-pitched diastolic murmur in the mitral area was considered to be an Austin Flint murmur. There was no chest or abdominal pain. As before, bed rest and digitalis therapy were temporarily effective. The third admission (service of Dr. S. Loewenberg) December 1, 1937, was again for decompensation. Roentgen-ray examination showed an aneurysm of the ascending arch of the aorta, but the serologic tests, as heretofore, remained negative. Pain in the lower abdomen was caused by distention of the bladder and was relieved by catheterization. Death on December 15, 1937, was due to progressive heart failure, the final diagnosis being syphilitic heart disease and prostatic hypertrophy.

*Case 2.* M. B., a colored woman, aged 69 years, was admitted to the Philadelphia General Hospital on the service of Dr. Robert Torrey, November 11, 1937, complaining of dyspnea of one month's duration. Mild ankle edema soon appeared. There was no substernal or precordial pain. There had been some blood spitting and occasional palpitation in the week preceding hospitalization. Her past medical history was otherwise irrelevant. Examination revealed an elderly but well preserved woman, markedly dyspneic and in congestive heart failure. The heart was greatly enlarged, especially to the left. The apical impulse was forceful and palpable as far out as the mid-axillary line. The rate was 96-100 per minute, in normal sinus rhythm. A blowing systolic apical murmur and a double aortic murmur were heard. The latter consisted of a short systolic and a pronounced blowing diastolic murmur. The area of the supracardiac dullness was widened and the blood pressure was 170/60 in both arms. Thoracentesis removed 2000 c.c. of transudate fluid from the right chest.

The liver was markedly enlarged, but leg edema had disappeared.

Laboratory data were not significant, except for repeatedly negative Kahn tests. An electrocardiogram revealed prolonged P-R intervals and occasional ventricular extra systoles. Fluoroscopic examination revealed a left ventricular enlargement and a markedly widened aortic arch. The clinical and roentgen findings led to a diagnosis of luetic heart disease, aortitis and aortic regurgitation. The advanced changes precluded specific therapy, and compensation was sufficiently restored by bed rest within one month to permit of the patient's discharge (December 13, 1937).

She was readmitted (January 7, 1938) with quickly recurring decompensation. The physical signs were as previously noted. An Austin Flint murmur and a Corrigan pulse were present. Repeated thoracenteses and digitalization were temporarily effective, but the patient had to return for a third time on April 13, 1938 because of decompensation. The Kahn tests were again repeatedly negative. Death occurred (June 30, 1938), after almost 9 months of recurring cardiac decompensation.

Necropsy (Dr. R. Philip Custer) revealed a healed dissecting aneurysm involving the entire aorta.

*Case 5.* A. S., a negro male, aged 65 years, was first admitted to the Philadelphia General Hospital November 23, 1933, on the neurological service of Dr. George Wilson, complaining of weakness in the left arm and leg. This began with a "stroke" in 1931, and six months prior to admission there was a similar episode involving the same side, but never resulting in complete paralysis. There were associated dizziness

cardiac decompensation is seldom encountered. The patients whose case histories were reported by Resnick and Keefer<sup>6</sup> and by Hamman and Apperly<sup>7</sup> lived long enough to enter an early phase of decompensation and therein the presence of a murmur of aortic insufficiency gave rise to a diagnostic problem.\* However, there was a history of severe pain in those cases which in the light of present knowledge would be considered suggestive of dissecting aneurysm. The pathogenesis of these murmurs remains obscure. That they have no basis in disease per se of the aortic valve leaflets has been demonstrated repeatedly at necropsy. On the other hand, they are unquestionably the result of the dissecting aneurysm in that no other lesion is demonstrable. In a recent interesting case report, the murmur was first noted 48 hours after the onset of severe chest pain, a matter of direct sequence.<sup>1</sup> It has been suggested that these murmurs are caused by (1) escape of blood from the original aortic channel similar to the mechanism of arterio-venous aneurysm (an explanation obviously inapplicable to chronic cases as above reported or to solely intramural dissection without rupture); (2) an imperfect closure of the aortic valve, due to distortion of the aortic ring by the nearby dissection (Hamman,<sup>7</sup> Wood<sup>8</sup>) or to loosening of the attachment of the aortic leaflet with resulting dislocation of the latter structure (Gravier,<sup>9</sup> Lundberg<sup>10</sup>). We were unable to demonstrate any definite alteration in alignment of the aortic leaflets. In each of our cases, however, the dissection progressed either down to the aortic valve or to a level immediately above the ring. We believe that this fact is important. It is our impression after reviewing almost all of the cases recorded since that of Letulle that a direct relationship exists between proximity of the dissection to the aortic ring and the development of the murmur of aortic insufficiency. Where such a murmur has been heard, the dissection had forced its way to within 2 cm., in a rare case 3 cm., from the aortic ring. We have not heard a diastolic aortic murmur or found one recorded in our case histories where dissection was later found to be limited to the thoracic or abdominal portions of the aorta. The actual extent of the dissecting aneurysm is irrelevant. An extensive "double-barrel" beginning in the aortic arch above the root of the aorta is not associated with signs of aortic valve insufficiency, whereas such signs may be pronounced and accompanied by cardiac failure in the case with a small dissection limited to the immediate supra-avalvular zone. The lesions may have been not only small, but entirely healed (see the case reports of Gallavardin and Gravier<sup>11</sup> and of Roberts<sup>12</sup>).

The mere proximity of the dissection to the aortic ring may be too simple an explanation. The immediate result of progressive dissecting hematoma at the root of the aorta would be to crowd and hamper the egress of blood from the left ventricle. This must occasionally occur in the early

\* The first clinical diagnosis in a case of dissecting aneurysm with aortic valvular insufficiency was made by Louis Hamman.